The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 2 SEPTEMBER, 1942 NUMBER 9

Treatment of Simmonds' Disease

ROBERT H. WILLIAMS, M.D. AND
JAMES L. WHITTENBERGER, M.D.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts

IT HAS NOW been almost 30 years since Simmonds (1) described the syndrome associated with extensive pituitary destruction. Since then, there have been many reports of the various clinical and pathological manifestations of this disease (2). In a number of the reports, however, the clinical diagnoses are not well established. The diagnosis is sometimes difficult to make and has, not infrequently, been missed. Nevertheless, with the methods now available for study, the diagnostic accuracy has increased.

Although in this report we are chiefly concerned with the treatment of Simmonds' disease, we will also emphasize certain diagnostic features, since the proper understanding of these increases the efficiency of treatment.

The disease is always associated with marked destruction of the anterior pituitary gland. The cause of the destruction is varied, although most commonly it is postpartum necrosis (3) or a tumor. As a result of this destruction there is a marked decrease in the function of the thyroid, adrenals and gonads. Thus, properly to seek out this group of patients when there is marked disturbance of the function of one of these glands, one must carefully investigate the state of the other two. Although failure of the thyroid, adrenals or gonads usually develops simultaneously, in some instances the evidence is clear that the onset of failure of the various functions may be separated by months or years.

We have listed below some of the clinical manifestations and tests which indicate hypofunction of the individual glands, realizing, of course, that some of these alterations are due to hypoactivity of several rather than of only one gland.

Pituitary. Local disturbances may be noted such as headaches, visual disturbances with demonstrable changes in the visual fields, enlargement and destruction of the sella turcica. These changes, however, are often absent. When the disease occurs in children, dwarfism is noted. The failure of the glands subsidiary to the pituitary is more manifest than the changes directly related to the pituitary.

Thyroid. All of the characteristics of primary myxedema may be present. In some instances, however, the basal metabolic rate may be much lower than the clinical state suggests. The basal metabolic rate is usually quite low, but it is sometimes normal, since at the time some patients are seen thyroid function has been preserved (*case* 3). The skin is sometimes smoother than normal. Generalized edema is usually present, although it is rarely sufficiently marked to permit pitting. The hair on the head may be of fine texture. The blood cholesterol tends to be slightly elevated. The plasma organic iodine is low. Bioassay of the urine for thyrotropic hormone reveals that none is present.

Received for publication July 22, 1942.

Adrenals. The cortical atrophy which results leads to the development of a clinical picture comparable to that of primary adrenal insufficiency.

Asthenia is one of the most common and pronounced manifestations. Mental changes frequently observed are depression, irritability and intolerance to pain. Hypoglycemic reactions develop at times. Not only does the general body hair decrease, but the axillary and pubic hair becomes scant or absent. In these patients we have never observed the type of pigmentation seen in Addison's disease. The blood pressure tends to be distinctly low and may drop further when the patient assumes an erect position. Mental disorientation or actual coma may be associated with the adrenal crises which sometimes develop. Anorexia, nausea, vomiting and abdominal cramps are apt to occur, particularly if infections are present, or if the patient is treated with thyroid.

The 17-ketosteroid excretion in the urine is markedly diminished, usually being less than 1 mg. per 24 hours (4). The serum sodium is definitely low in most cases, but in some instances, in order to demonstrate a disturbance of sodium metabolism, it is advisable to perform a sodium deprivation test such as the one described by Cutler, Power and Wilder (5, 6). The two procedures reported by Robinson, Power and Kepler (7) are useful and somewhat more simple than the foregoing test. These procedures depend upon the principle that patients with Addison's disease *a*), do not experience a normal diuresis following the rapid intake of a considerable quantity of water, and *b*), they tend to excrete excessive amounts of sodium chloride but retain urea. The serum potassium is sometimes elevated. The fasting blood sugar is occasionally low, but the defect in carbohydrate metabolism is best demonstrated by means of the insulin tolerance test. With this test one can almost invariably show insulin sensitivity and hypoglycemia unresponsiveness; i.e., in these patients there is a more marked fall in the blood sugar than in normal individuals and an impaired return to the fasting level (8).

Gonads. a) Male. There is loss of libido, impotence, scanty beard, decreased body hair, atrophy and weakness of muscles. The penis, testicles and prostate are small. The 17-ketosteroids are quite low and there is little or no follicle-stimulating hormone[1] in the urine. *b) Female.* There is loss of libido, sterility, amenorrhea (not associated with menopausal symptoms) and atrophy of the genitalia. The breasts are normal or small. Little, if any, follicle-stimulating hormone is present in the urine.

General considerations. Hypopituitarism may occur at any age, although most commonly during middle age; it is more common in females. An anemia is often present which does not respond to iron or liver. The condition is most frequently confused with anorexia nervosa, malnutrition with anemia or primary involvement of the subsidiary glands (thyroid, adrenals, gonads). We believe, however, that it can be accurately differentiated in most instances if studies are made and the data are considered collectively.

Not only has difficulty been encountered in the diagnosis of Simmonds' disease, but its treatment has been very unsatisfactory. Anterior pituitary extracts of various kinds, pregnant mare serum gonadotropin, thyroid, testosterone, adrenal cortical extract and many other substances have been used (2, 9, 10). The pituitary extracts usually have very little effect and usually produce an antihormone reaction. Of course, the use of pituitary extracts would seem to be the logical form of treatment, but since up to the present time they have failed, the next step is to use certain products of the subsidiary glands, (such as ovarian extracts and desiccated thyroid) hoping to secure a good balance between them. Thyroid, when given alone, usually does not cause much improvement and, indeed, not infrequently induces an adrenal crisis (9). It is not surprising that the symptoms of adrenal insufficiency become more obvious under thyroid treatment, since it promotes excretion of sodium and water (11, 12). This effect can be counteracted by the simultaneous utilization of sodium chloride and desoxycorticosterone, the exact amount necessary being assayed on each individual case. The implantation of pellets would seem advantageous because of convenience, efficiency and economy. From previous experience we have learned that some of these patients, after correction of the metabolic rate and of the water and electrolyte balance, still lack energy and strength. Consequently, since testosterone has been shown to cause a retention of sodium (13, 14), potassium (14, 15), nitrogen (15, 16, 17) and water, and since it increases the muscle mass (18) and strength, it seemed advisable to use it, in the form of pellets, in conjunction with the thyroid and adrenal treatment. Of course, in males it also tends to correct some of the gonadal disturbances. Testosterone in large doses causes elevation of the basal metabolic rate (19), but in doses of from 10 to 20 mg. daily does not affect it very much. Desoxycorticosterone acetate does not have an appreciable effect on the basal metabolic rate (20).

With these facts in mind, during the past year we have treated 5 unselected cases of Simmonds' disease with thyroid extract,[2] desoxycorticosterone acetate,[3]

[1] When gonadal failure is primary, the 24-hour excretion of follicle-stimulating hormone in the urine is much greater than 10 R.U., but when the failure is on the basis of pituitary insufficiency, it is usually less than 10.

[2] All of the thyroid used conformed to the U.S.P.

[3] The pellets of desoxycorticosterone acetate (Doca) were

sodium chloride and testosterone.[4] All patients were hospitalized. We give the case reports below.

CASE ABSTRACTS

Case 1 (#1047166). A housewife, aged 42, was admitted in May, 1941, because of myxedema. She had never been well since she had placenta praevia with marked blood loss at the birth of her sixth child, 12 years previously. She was always pale and weak thereafter and never menstruated again, but had no hot flashes. A few months after delivery she became nervous, cried readily and later noted persistent drowsiness, sensitivity to cold, dry scaly skin, puffiness of face, hands and feet, loss of hair from axillae and pubis, thick speech, coarse voice and brittleness of nails. All teeth 'just fell out.' Occasional spells of nausea, vomiting and abdominal cramps occurred. The patient had taken thyroid extract for intervals of months for 10 years. Thyroid extract caused the basal metabolic rate to return to normal, yet the patient did not feel well, always lacking strength and energy. She occasionally had spells, unrelated to meals, when she developed weakness and faintness and sometimes nausea and vomiting. She also had other attacks which seemed to be hypoglycemic reactions, since they were characterized by weakness, nervousness, faintness and intense hunger and were readily relieved by the ingestion of food. For several years she had led an essentially vegetative existence.

On examination, the patient showed marked slowing of her mental and physical activities. The nutritional state was good, the weight 122 pounds (fig. 1). Her voice was coarse and low pitched, and the tongue thick. The skin was pale, dry, cool, scaly, puffy and inelastic. Hair on the head was fine and soft but thinned; eyebrows were sparse; there was no axillary or pubic hair. There was dorsal kyphoscoliosis. Breasts were normal. Genitalia were atrophic. Blood pressure was systolic, 90 and diastolic, 50 mm. Hg.

Significant laboratory data were: red blood cells 3,500,000; hemoglobin 71 per cent; white blood cells 2100; follicle-stimulating hormone, negative to 10 R.U.; 17-ketosteroids, 0.3 mg. per 24 hours; basal metabolic rate, −43 per cent; blood lipids, 2400 mg. per cent; cholesterol, 262 mg. per cent; serum sodium, 133 m.eq. per liter (normal 140 to 142); serum potassium, 5.8 m.eq. per liter. Roentgenograms of the skull showed the sella turcica to be slightly smaller than normal. Plasma protein iodine was less than 1 microgram per cent (normal 4 to 8). Insulin tolerance test, marked sensitivity to insulin, the blood sugar falling to 28 mg. per cent 30 minutes after the injection, intravenously, of 2 units of insulin (fig. 2). Urinary thyrotropic assay was negative. Gastric analysis showed no free acid in the fasting contents, even after the subcutaneous injection of 0.5 mg. of histamine phosphate.

On June 11 she was given 1 cc., intramuscularly, of thyrotropic hormone.[5] Within an hour there was marked pallor, weakness and severe pain in the abdomen and neck. An intradermal test on the same day, using 0.1 cc. of the same preparation, had been negative. Another preparation of thyrotropic hormone[6] given in intramuscular doses of 1 cc. daily for a period of 2 weeks, had no definite effect on the basal metabolic rate. Intradermal sensitivity to a test dose of anterior pituitary extract[7] prevented its use in treatment.

Fig. 1. *Case 1.* NOTE GOOD NUTRITIONAL STATE, myxedematous facies, normal breast and absence of hair.

On December 29, treatment was begun with sodium chloride, 5 gm. daily; methyl testosterone, 10 mg. three times daily; desoxycorticosterone acetate,[8] 2 mg. daily,

supplied through the kindness of Dr. E. Oppenheimer of the Ciba Pharmaceutical Products, Inc., Summit, N. J., and Dr. G. W. Thorn of the Peter Bent Brigham Hospital, Boston, Mass. Each pellet weighed approximately 125 mg.

[4] The tablets of methyl testosterone (Oreton-M) and the pellets of testosterone (Oreton-F) were supplied through the courtesy of Dr. M. Gilbert of the Schering Corp., Bloomfield, N. J. Each pellet weighed approximately 150 mg.

[5] The thyrotropic hormone (antuitrin-T) was supplied by Parke, Davis Co., Detroit, Mich.

[6] This preparation of thyrotropic factor was supplied by Armour Laboratories, Chicago, Ill.

[7] The anterior pituitary extract (Polyansyn) was supplied by Armour Laboratories, Chicago, Ill.

[8] The desoxycorticosterone acetate (Doca) was supplied by Roche-Organon, Inc., Nutley, N. J.

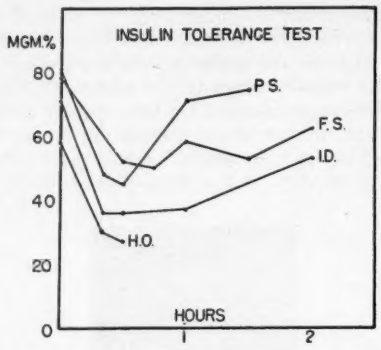

Fig. 2. Response of blood sugar following injection of 2 to 3 u of insulin intravenously. Note rapid fall in blood sugar and in two cases the hypoglycemic unresponsiveness.

intramuscularly; and thyroid, 0.5 grain daily. The dosages of these medications were varied in accordance with the clinical status of the patient and the significant laboratory findings (fig. 3). At the time of discharge from the hospital (March 7), the patient possessed subcutaneous implantations of 2 pellets of testosterone and 1 of desoxycorticosterone acetate. She was also taking thyroid, 1 grain daily, and sodium chloride, 2 gm. daily.

The patient demonstrated a marked increase in strength, energy and feeling of well-being. She stated that she felt distinctly better than she had for 12 years. She no longer had any complaints and the myxedematous manifestations disappeared (fig. 4). There was a moderate growth of hair in the axillae and pubis. The growth of hair on the head also increased.

We have examined her at frequent intervals during the past 4 months, since her discharge from the hospital, and have observed continued improvement and no ill effects.

Case 2 (#1047262). A white laborer, aged 46, was admitted to the hospital in August, 1941, complaining of weakness and dizziness. For 5 years he had noted gradually increasing weakness and fatigability. very scanty beard, impotence, lack of libido, slowing of mental and physical activities, sensitivity to cold and irritability. He

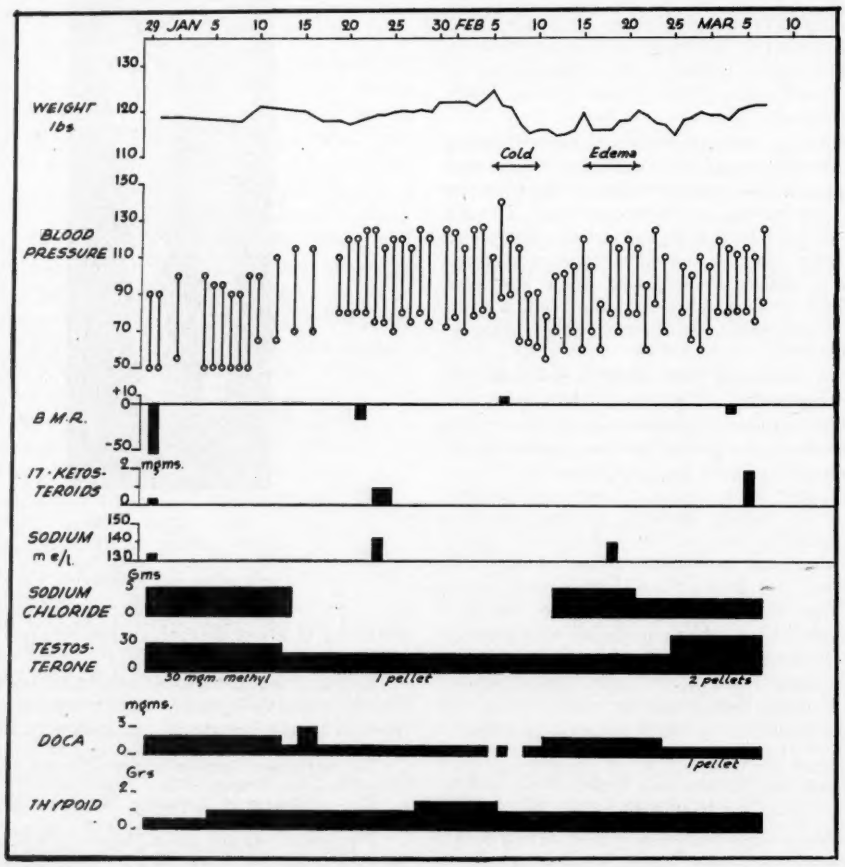

Fig. 3. Response to treatment in *case 1*.

Fig. 4, *A. Case* 1. NOTE SIMILARITY OF FACE to that in primary myxedema. *B.* NORMAL APPEARANCE one month after beginning treatment.

was treated with thyroid extract for 1.5 years with no appreciable benefit. Three months before admission, he noticed increased weakness and fatigability, with development of unsteady gait. Three weeks before admission the dosage of thyroid was increased to 2 grains per day. Shortly thereafter he developed marked weakness, nausea, vomiting, headache and blurred vision.

Examination showed a relatively good nutritional state, weight 171 pounds (fig. 5), poor strength and slowing of the mental and physical activities. The skin was pale, pasty, smooth and cool; eyelids were puffy. There was no hair on chest, arms and legs and only a small amount on face, pubis and axillae. Penis, testicles and prostate were less than half of normal size. Blood pressure was 104 mm. Hg. systolic and 70 diastolic.

Laboratory examinations showed: Basal metabolic rate, −25; follicle-stimulating hormone, negative to 10 R.U. per 24 hours; 17-ketosteroids, 2.5 mg. per 24 hours. Bioassay of the urine for thyrotropic hormone was negative. Serum sodium was 127.4 m.eq. per liter and serum potassium 5.0 m. eq. per liter. Insulin tolerance test revealed increased sensitivity to insulin (fig. 2). Roentgenogram of skull showed expansion and erosion of the sella turcica. Visual fields were normal. Roentgen treatment to the pituitary (200 roentgen units every 2 days for 20 days), given from September 5 to 30, resulted in no definite improvement. Nausea and vomiting were very troublesome during the course of treatment, in spite of the administration of yeast, nicotinic acid and sodium chloride.

In the succeeding 3 months there was a distinct increase in weakness, mental depression, anorexia, nausea and vomiting. Basal metabolic rate fell to −36 per cent. Blood pressure fell to 74 mm. Hg. systolic and 56, diastolic.

Fig. 5. *Case* 2. GOOD NUTRITIONAL STATE; myxedematous facies.

A polyvalent anterior pituitary extract[7] was given in doses of 1 cc. three times daily, intramuscularly, from December 4 to 18, but no beneficial effects were noted.

On December 26, treatment was begun with sodium chloride, 5 grams daily; thyroid extract, 0.5 grain daily; methyl testosterone, 10 mg. three times daily; and desoxycorticosterone acetate,[8] 2 mg. daily (fig. 6). It was necessary to raise the dosage of thyroid to 2 grains daily. At the time of discharge (March 6) he possessed subcutaneous implantations of 5 pellets of desoxycorticosterone acetate and 3 of testosterone. The blood pressure, basal metabolic rate and serum sodium returned to normal levels. The patient changed from a weak, constantly complaining, depressed individual to one who was active and strong. He developed a heavy growth of hair over the body. The penis, testes and prostate increased in size. His strength and libido increased so much that he was having coitus 3 times a week.

He has been seen at 2 to 3-week intervals for the past 3 months. The added salt was discontinued because the blood pressure was slightly elevated; following the decrease in salt intake the pressure returned to normal.

Case 3 (#1048285), a female artist, aged 37, was admitted in May, 1941, complaining of headaches and blurred vision. She had had a 'nervous breakdown' 10 years previously with subsequent irritability and slight depression, and 5 years later (1936) developed a few attacks of asthma. At about the same time the menses ceased and did not recur; there were no hot flashes. During the year preceding admission she noted easy fatigability, weakness, sensitivity to cold, dryness of hair, headache and blurring of vision. Her weight did not vary.

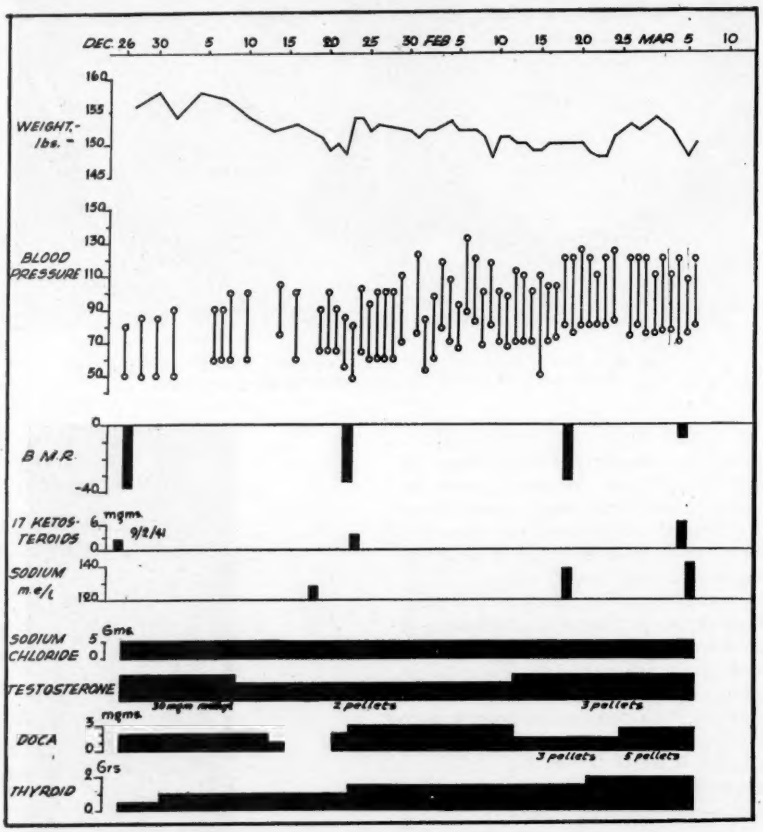

Fig. 6. Response to treatment in *case* 2.

On examination she was found to be a weak individual, somewhat insensitive to psychogenic influences, but hypersensitive to pain. General nutrition and development were relatively good (weight, 118 pounds). Skin was pale, dry, scaly and cool; eyelids were puffy. Hair was fine and dry; it was scanty on pubis. In the left eye visual acuity was much impaired and the optic disc was pale; visual field determination revealed bitemporal hemianopsia. Blood pressure was 90 mm. Hg. systolic and 60, diastolic.

Laboratory studies revealed: Red blood cells 5,000,000; hemoglobin, 97 per cent; white blood cells 6400. Fasting blood sugar, 87 mg. per cent; blood chlorides, 99 m. eq.

per liter. Basal metabolic rate, −9 per cent. Roentgen-ray examination of skull showed marked depression and erosion of the floor of the sella; erosion and posterior displacement of the posterior clinoidal processes.

A diagnosis of chromophobe adenoma was made and roentgenotherapy applied, 200 roentgen units daily for 20 days. She was discharged in June, but was readmitted in August because no improvement resulted. Nausea and vomiting occurred at intervals. The results of examination were the same as in May, except that the disturbances were slightly more marked. The serum sodium was 132 m. eq. per liter; 17-ketosteroids, 0.4 mg. per 24 hours; follicle-stimulating hormone, negative to 10 R. U.; basal metabolic rate, −10 per cent. Another course (4000 roentgen units) of roentgenotherapy was given over the pituitary. Weakness, nausea and vomiting became pronounced. The blood pressure remained at a lower level and upon one occasion dropped to 60 mm. Hg systolic and 40, diastolic, with general symptoms of shock.

She was then treated daily with 5 gm. of sodium chloride and with from 4 to 6 mg. of desoxycorticosterone acetate. Definite improvement in the clinical state resulted and the serum sodium returned to normal levels, but she continued to be weak. She remained at home from October 4 until November 30, taking salt but no hormone. Weakness, dizziness and headache persisted and occasionally she had nausea and vomiting. Upon her return to the hospital a further decrease in visual fields was found. The blood pressure was 90 mm. Hg systolic and 60, diastolic; red blood cells, 3,700,000; hemoglobin, 72 per cent; white blood cells, 5700; serum sodium, 128 m. eq. per liter; serum potassium, 4.3 m. eq. per liter; and basal metabolic rate, −30 per cent.

Daily administration of 10 gm. of sodium chloride caused only slight improvement in her condition. She was so weak that she remained in bed all of the time and was fed by the nurses. On January 9, treatment was begun with sodium chloride, 8 gm. daily; methyl testosterone, 10 mg. 3 times daily; desoxycorticosterone acetate, 3 mg. daily, intramuscularly; and thyroid, 0.5 grain daily (fig. 7). Within a few days the anorexia, nausea and vomiting disappeared. There was so much increase in strength and energy that the patient began to exercise a great deal in the ward and experienced a feeling of well-being for the first time in several months. Gain in weight was rapid. Because of the persistence of hypothyroid symptoms and a low basal metabolic rate, the dosage of thyroid extract was increased to one grain daily. The dosage of desoxycorticosterone acetate was reduced to 2 mg. daily, but an associated fall in blood pressure made it necessary to resume the original dose. With cessation of the methyl testosterone for 6 days there was a definite loss of energy and strength. Associated with the development of a marked bronchitis there was a drop in the blood pressure,

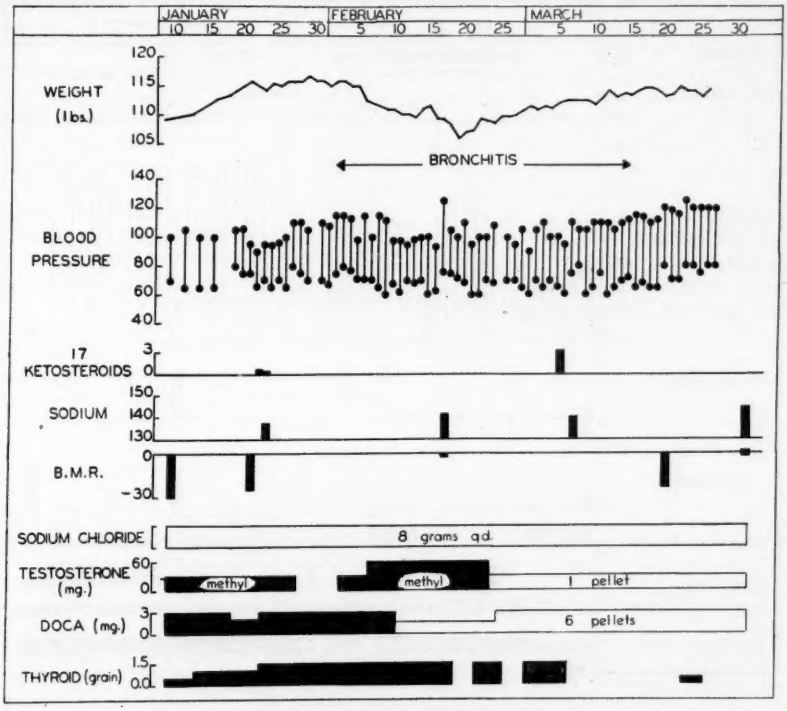

Fig. 7. Response to treatment in *case* 3.

loss of weight and a partial return to the previous clinical state. With the disappearance of infection she showed remarkable improvement. The thyroid was temporarily discontinued since it was thought to be a factor in the persistence of a low-grade fever. Liver extract,[9] 1 cc. daily for 3 days, caused no appreciable change in the blood picture, but at the time of discharge the hemoglobin was 85 per cent, red blood cells 4,100,000 and hematocrit 36.5 per cent. She was finally regulated with sodium

body, lasting only a few days. Menses ceased 10 years previously (1924) without hot flashes or other menopausal symptoms. She was known to have had a normocytic anemia of undetermined etiology for 7 years.

Physical examination demonstrated normal size and development (weight 117 pounds); dry, inelastic, atrophic, cool skin; scanty growth of hair on pubis, axillae and eyebrows; thin, brittle, spoon-shaped nails; and a blood pressure of 140 mm. Hg. systolic and 70, diastolic.

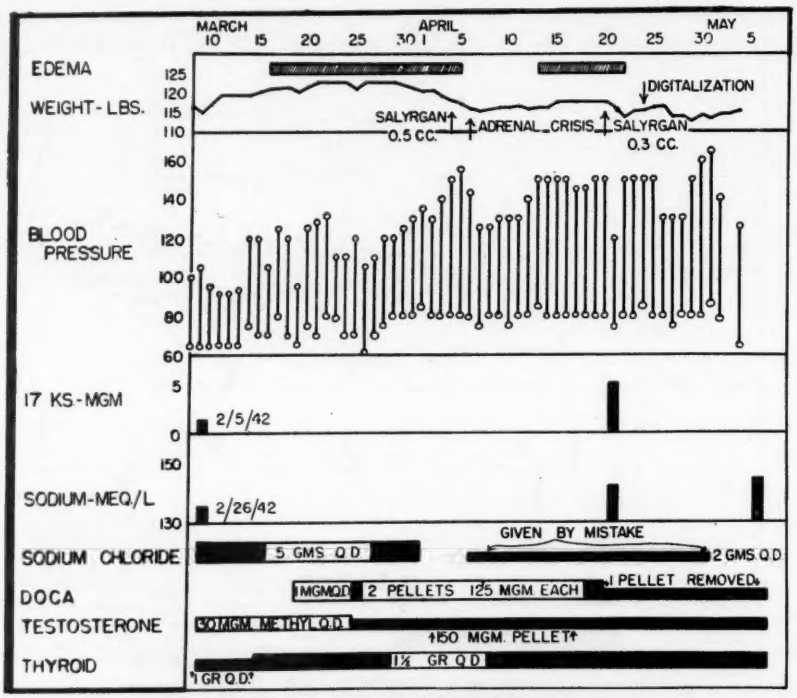

Fig. 8. Response to treatment in *case 4*.

chloride, 8 gm. daily, 1 pellet of testosterone, 6 pellets of desoxycorticosterone acetate and thyroid, 0.5 grain daily. With this regimen the strength and general feeling were excellent and the blood pressure, sodium and basal metabolic rate were normal. She was discharged April 1. When seen again in May the progress had been excellent. There remained marked narrowing of the visual fields. Resection of the tumor was recommended, but the patient felt so well that she refused.

Case 4 (*#1058888*). A single white woman, aged 60, was admitted to the hospital in 1934, complaining of shortness of breath on exertion. Eight weeks before admission she noticed a sensitivity to cold weather and soon thereafter loss of appetite, weakness, dizziness, falling of hair and exertional dyspnea. Three weeks before admission she developed anesthesia of the left side of the

[9] The liver extract (Reticulogen) was supplied by Eli Lilly & Co., Indianapolis, Ind.

The red blood cell count was 3,500,000; hemoglobin, 69 per cent; reticulocytes, 0.6 per cent; hematocrit, 30 per cent; cholesterol, 247 mg. per cent; basal metabolic rate, −20 per cent. No free acid in gastric juice even after the injection of 0.5 mg. of histamine.

No appreciable change in the hemoglobin, red blood cells or reticulocytes followed intensive treatment with iron, liver and thyroid. With 3 grains daily of thyroid for 5 weeks there was no change in the blood counts. The basal metabolic rate rose to −7 per cent, but the patient experienced several attacks of anorexia, nausea, vomiting, abdominal cramps and diarrhea. The weight dropped from 115 to 106 pounds and the blood pressure dropped to 105 mm. Hg systolic and 70, diastolic. For the next 6 years she took thyroid irregularly, but never felt very well. She was bothered at times with sensitivity to cold, anorexia, nausea, vomiting, abdominal cramps, weakness, dizziness, headaches and occasional angina pectoris.

She was readmitted to the hospital in January, 1942,

complaining chiefly of anorexia, weakness, dyspnea and edema. The findings in the physical examination were similar to those in 1934.

The red blood cell count was 4,200,000; hemoglobin, 68 per cent; basal metabolic rate −33 per cent; 17-ketosteroids, 1.4 mg. per 24 hours; follicle-stimulating hormone, negative to 20 R.U. The insulin tolerance test showed hypersensitivity to insulin, with an impaired hypoglycemic response (fig. 2). The protein iodine was 3 micrograms per cent; serum sodium 135.6 m. eq. per liter. In roentgenograms the sella turcica appeared normal.

On March 9, 1942, treatment was started with daily doses of 5 gm. of sodium chloride, 30 mg. of methyl testosterone and 1 grain of thyroid extract (fig. 8). Within a few days there was an increase in strength and in blood pressure. Slight edema of the ankles developed, but the patient had had this occasionally before treatment. At times the blood pressure was low, so 1 mg. of desoxycorticosterone acetate per day was given. On March 25, 2 pellets of desoxycorticosterone acetate and 1 of testosterone were implanted. The blood pressure continued to rise, the edema increased and râles appeared over the lower half of the chest. Discontinuance of the extra salt did not have much apparent effect, so 0.5 cc. of salyrgan was given. The edema disappeared, but there was an adrenal crisis (drop of blood pressure, nausea, vomiting, diarrhea, abdominal cramps and marked weakness). Within a few days the edema and elevated blood pressure again returned. One pellet of desoxycorticosterone acetate was removed. The administration of 0.3 cc. of salyrgan again caused disappearance of the edema and a drop in blood pressure, but these changes were only transitory. A similar response occurred with digitalization. On April 30 it was discovered that, by mistake, she had been receiving 2 gm. of added salt daily for the preceding 3 weeks. When this was stopped the blood pressure returned to normal and no more edema developed, in spite of the discontinuance of digitalis.

At the time of discharge from the hospital the patient was receiving 1.5 grains of thyroid per day and had implantations of 1 pellet of testosterone and 1 of desoxycorticosterone acetate. At this time the blood pressure, basal metabolic rate, serum sodium and 17-ketosteroid excretion and blood counts were normal. During her stay in the hospital she experienced marked improvement. There was a distinct increase in strength, energy and ambition and she had no more complaints. A very slight beard appeared, but this had not been noticed by the patient.

When seen again, 2 weeks later, the blood pressure was 160 mm. Hg systolic and 90, diastolic; 4 weeks later it was 185 mm. Hg systolic and 95, diastolic. No edema had developed and there was no gain in weight, but she had been bothered with headaches, slight exertional dyspnea and orthopnea. The pellet of desoxycorticosterone acetate was removed on June 5; following this the blood pressure became normal and she felt well in every way.

Case 5 (#764228). *F. S.*, aged 45, was admitted to the Evans Memorial Hospital[10] (#286299) December, 1941, in a confused state. She had not felt very strong for about 20 years, following a panhysterectomy for a pelvic inflammatory disease. She was admitted to the Boston City Hospital in 1934, complaining of pronounced weakness, easy fatigability, drowsiness and weight loss of 2 years' duration. She had had occasional spells of anorexia, nausea and vomiting. On one occasion her family physician found a blood pressure of 84 mm. Hg systolic. Examination, in 1934, showed pallor of skin, slowing of mental and physical activities, scoliosis, hyperactive deep reflexes and equivocal Babinski reactions. The red blood cell count was 3,000,000; hemoglobin, 60 per cent; hematocrit, 28 per cent; mean corpuscular volume, 90 cubic micra. Kahn, doubtful. Follicle-stimulating hormone, negative. Glucose tolerance test, using 100 grams of glucose by mouth: fasting 79 mg. per cent; 30 minutes, 103; 1 hour, 105; 1.5 hours, 107; 2 hours, 111. The basal metabolic rate was −21 per cent. Gastric analysis revealed no free acid in fasting contents.

Adequate doses of iron, liver and thyroid caused no appreciably change in the blood picture. The basal metabolic rate returned to normal levels, but no improvement in the clinical state occurred. In association with the treatment with thyroid she developed an increase in the pulse rate, a drop in blood pressure and nausea, vomiting and diarrhea.

During the subsequent 8 years weakness and fatigue remained prominent. Two weeks preceding admission she developed nausea and often vomited; diplopia also appeared. On the day before admission she was disoriented as to time and place.

Examination revealed a fairly good general state of nutrition (weight 122 pounds) and development; clouded sensorium; slurred speech. The skin was pale, dry, smooth and atrophic. Hair was dry; no hair on arms or legs; the hair in axillae, on pubis and eyebrows was sparse. There was marked dorsal kyphosis. There was slight weakness of the muscles supplied by the left sixth and seventh nerves; bilaterally positive Babinski, Oppenheim, Chaddock and Gordon signs; hyperactive reflexes of extremities; spasticity of legs. Breasts were normal. Blood pressure was 108 mm. Hg systolic and 76, diastolic. There was slight edema of the legs.

The laboratory studies revealed that the blood picture was the same as before; basal metabolic rate, −32 per cent; hippuric acid, 1.2 gm.; Hinton test on serum and spinal fluid, positive; protein of cerebrospinal fluid increased but no increase in cells. The water test (7) for adrenal insufficiency was positive, but the Wilder test (5) was negative. The insulin tolerance test (3.5 U intravenously) showed a hypoglycemic unresponsiveness (see fig. 2). At the end of 1 hour there was marked sweating, drowsiness, fatigue and mental confusion. The test for follicle-stimulating hormone was negative; 17-ketosteroids, 0.2 mg. per 24 hours; serum sodium 127 m. eq. per liter; cholesterol, 167 mg. per cent. Roentgenograms of the skull showed that the sella turcica was small, but otherwise normal. There was decalcification and kyphosis of the dorsal spine.

On January 9, treatment was begun with thyroid, 0.5 grain daily. The dosage was progressively increased until

[10] The authors are indebted to Doctors Keefer, Moss and Oliver for the opportunity of following the course of this patient.

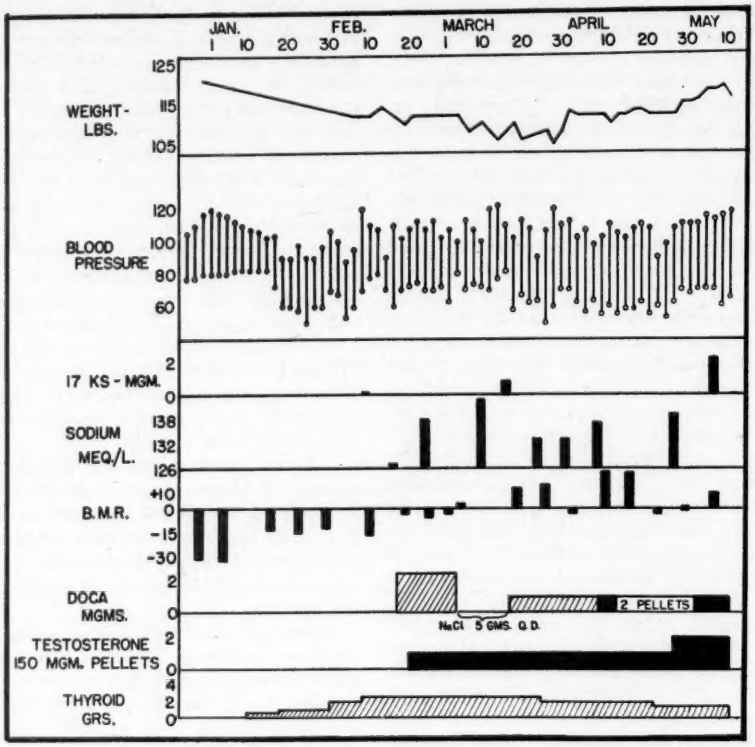

Fig. 9. Response to treatment in *case* 5.

2.5 grains per day were given. With this treatment there was a rise in the basal metabolic rate to normal, but there was a distinct fall in weight and blood pressure and no improvement in the patient. She was finally regulated with subcutaneous implantations of 2 pellets of desoxycorticosterone acetate, 2 pellets of testosterone and 1.5 grains of thyroid by mouth per day (fig. 9). At the time of discharge (May 12) the blood pressure, serum sodium and basal metabolic rate were normal. The patient had experienced a marked increase in strength. She felt well in every way and had no complaints. The slight anemia persisted. No excess of hair growth occurred.

DISCUSSION OF CASES

Clinical Characteristics

History. Of the 5 patients treated, there were 4 females and 1 male, with ages ranging from 37 to 60 years (table 1). At the time that we were consulted, these patients had had their disease for intervals of 5 to 20 years. None of the patients had had any sexual activity for several years. The females had had amenorrhea for a long time but none had experienced menopausal reactions. All had clear-cut symptoms of

Table 1. Significant clinical data on patients with Simmonds' disease

Case No.	Etiology	Age years	Sex	Duration of Symptoms years	Sex Activity	Hot Flashes	Blood Pressure, mm. Hg	Adrenal Crisis	Myxedema
1	Postpartum necrosis	42	F	12	0	0	90/50	+	+
2	Chromophobe adenoma	46	M	5	0	0	74/65	+	+
3	Chromophobe adenoma	37	F	5	0	0	90/60	+	+
4	? Thrombosis	60	F	8	0	0	100/65	+	+
5	? Syphilis	45	F	20	0	0	105/75	+	+

myxedema. Four had been diagnosed as having myxedema and had received thyroid treatment irregularly for several years. In association with this treatment, each had experienced attacks of anorexia, nausea, vomiting and weakness. Abdominal cramps and diarrhea were sometimes present and one patient became totally disoriented. In none of the cases was either the patient or the physician satisfied with the thyroid treatment. There was a response in the basal metabolic rate, but the patient would not feel very well and therefore took the thyroid very irregularly. Three patients experienced symptoms of marked adrenal insufficiency even without thyroid treatment. Three had had spontaneous hypoglycemic reactions. All were bothered with weakness and lack of energy. Two patients had gained weight in the course of the disease, 2 had remained of the same weight and 1 had lost a small amount. All tended to be depressed and irritable and none had done more than a trivial amount of work for a long time. Three had been found to have anemia several years previously, and had taken iron and liver without benefit.

Physical examination. Contrary to the usually emphasized chief characteristic of this disease, cachexia, none of our patients was cachectic. Furthermore, in only 1 of the 8 other cases of Simmonds' disease whom we have studied, was this manifestation present. The general nutritional state appeared relatively good (fig. 1, 5). In 2 patients the changes of myxedema were classic (fig. 4, A), whereas in the others they were present although not so marked. In all, the skin was cool and puffy. In 3 it was rough, but in the other 2 it was smoother than in normal individuals. The hair on the head was slightly thin and fine. There was little, if any, axillary or pubic hair, and essentially no hair on the trunk. There was no atrophy of the breasts. The internal and external genitalia were atrophic. The blood pressure ranged from 76 to 105 mm. Hg systolic, and from 65 to 75, diastolic.

TABLE 2. SIGNIFICANT LABORATORY STUDIES IN PATIENTS WITH SIMMONDS' DISEASE

Case No.	B.M.R. %	FSH	17 Keros-teroids mg./24 hr.	Serum Sodium m.e. per liter	X-ray of Sella
1	−43	0	0.3	133	Negative
2	−36	0	2.5	127	Tumor
3	−30	0	0.4	127	Tumor
4	−33	0	1.4	136	Negative
5	−32	0	0.2	127	Negative

Laboratory studies. The basal metabolic rate was −30 per cent, or below, in each case (table 2). The plasma organic iodine, determined in 2 cases, was found to be in the range characteristic for myxedema. No thyrotropic hormone was found in the urine of 2 subjects. The serum sodium ranged from 127 to 136 m. eq. per liter (normal 140 to 142). The excretion of 17-ketosteroids in the urine was quite low (0.2 to 2.5 mg. per 24 hours). No follicle-stimulating hormone was found in the urine, tested for 10 R.U. in 4 cases, for 20 R.U. in 1 case. The insulin tolerance test, performed with 4 patients, using from 2 to 3 U of insulin intravenously, showed an insulin sensitivity and in 2 there was an impaired hypoglycemic response. Roentgenograms of the skull revealed in 2 subjects changes in the sella turcica, interpreted as being due to a pituitary tumor.

TABLE 3. TREATMENT WHEN DISCHARGED FROM HOSPITAL

Case No.	Thyroid, gr.	Testosterone, 150-mg. pellets	Desoxycorti-costerone Acetate, 125-mg. pellets	NaCl, gm. q. d.
1	1	2	1	3
2	2	3	5	0
3	½	1	6	8
4	1½	1	1	0
5	1½	2	2	0

Treatment

Regulation of medication. As may be seen on the individual charts of the cases of the patients (fig. 3, 6, 7, 8 and 9), the adequate regulation of the doses of the various hormones is attained only after careful and prolonged observation of the patients. Most of the difficulty encountered is in the estimation of the number of pellets of desoxycorticosterone acetate which are necessary, because it sometimes takes several weeks to note their full effect. Desoxycorticosterone acetate in oil was used in conjunction with the thyroid and testosterone. The amount of desoxycorticosterone acetate necessary to maintain a normal weight, blood pressure and blood serum was regarded as the adequate quantity. We attempted to give enough desoxycorticosterone so that only a small amount of extra salt was necessary. Thereby, the patient would be prepared for respiratory infections or any other added burdens by merely increasing his ingestion of salt. The effects of respiratory infections may be noted in *cases* 1 and 3. At the time of discharge the number of pellets of desoxycorticosterone acetate used varied from 1 to 6, 125 mg. each (table 3). One patient was discharged with instructions for taking 3 grams of salt daily, another was taking 8 grams daily, while none was prescribed for the other three.

The amount of thyroid necessary was a much more simple problem. The initial dose of thyroid was 0.5 grain and this was increased until, by clinical observation and according to the basal metabolic rate, there was no evidence of thyroid insufficiency. The

ultimate dosage varied from 0.5 to 2 grains. The more the thyroid was increased, the more the desoxycorticosterone acetate had to be increased.

With the females the aim as regards the use of testosterone was to use enough to secure a marked increase in strength, energy and general well-being without obtaining masculinization. This usually required 1 or 2 pellets (150 mg. each). The dosage for the male was governed not only by these general reactions but also by the amount of sexual stimulation. Three pellets were required in his case.

Each of the patients was given small amounts of food between meals and at bed-time in order to distribute the supply of carbohydrates evenly over the 24 hours, thereby preventing hypoglycemic reactions.

Results of treatment. In all 5 cases the blood pressure, basal metabolic rate and serum sodium have returned to normal and have remained there. The myxedematous manifestations have disappeared. In each subject there has occurred a marked increase in strength, energy and ambition. The mental state has changed from a dull, irritable and depressed level to an alert and cheerful one. All have developed a marked increase in the desire and the capacity for work. None of the symptoms of adrenal insufficiency has reappeared. The 17-ketosteroid excretion increased in each case, varying from 2 to 6 mg. per 24 hours. The weight curves varied somewhat, but had a tendency to increase with the institution of treatment. There were counterbalancing actions of the drugs, however, the thyroid promoting loss of weight in part by its diuretic action, whereas the testosterone and desoxycorticosterone acetate promoted gain in weight due to the retention of water and sodium and to the increase in muscle mass.

Of the 3 patients with normocytic and normochromic anemia, none of whom had responded to iron or liver, the anemia has disappeared in two. If this response is directly related to the hormone treatment, it possibly is due to the testosterone, since thyroid had been tried previously without benefit.

The 60-year-old woman described in *case 4* did not tolerate very much desoxycorticosterone acetate, reacting with slight hypertension and edema. There is very good evidence, however, that she had adrenal insufficiency. She had previously had attacks of angina pectoris with mild cardiac failure. Therefore, it is our impression that the adrenal insufficiency tended to prevent her from having cardiac failure, but when this was corrected the latter became apparent.

In no case was there enough overgrowth of hair to cause concern.

SUMMARY

Five cases of Simmonds' disease have been treated with desoxycorticosterone pellets, testosterone pellets and thyroid. The results have been gratifying in each case. In each there was a marked increase in strength, energy and feeling of well-being. The blood pressure, basal metabolic rate and serum sodium returned to normal. No significant ill-effects resulted from the treatment.

The dosage of the various substances must be determined individually in each case.

REFERENCES

1. Simmonds, M.: Ueber hypophysisschwund mit todlichem Ausgang. *Deutsche med. Wchnschr.* 40: 322. 1914.
2. Escamilla, R. F., and H. Lisser: Simmonds' disease. A clinical study with review of the literature; differentiation from anorexia nervosa by statistical analysis of 595 cases, 101 of which were proved pathologically. *J. Clinical Endocrinology* 2: 65. 1942.
3. Sheehan, H. L.: Simmonds' disease due to post-partum necrosis of the anterior pituitary. *Quart. J. Med.* 8: 277. 1939.
4. Fraser, R. W., A. P. Forbes, F. Albright, H. Sulkowitch and E. C. Reifenstein, Jr.: Colorimetric assay of 17-ketosteroids in urine. A survey of the use of this test in endocrine investigation, diagnosis and therapy. *J. Clinical Endocrinology* 1: 234. 1941.
5. Cutler, H. H., M. H. Power and R. M. Wilder: Concentrations of chloride, sodium and potassium in urine and blood: Their diagnostic significance in adrenal insufficiency. *J. Am. Med. Assoc.* 111: 117. 1938.
6. Stephens, D. J.: Chloride excretion in hypopituitarism with reference to adrenocortical function. *Am. J. M. Sc.* 199: 67. 1940.
7. Robinson, F. J., M. H. Power and E. J. Kepler: Two new procedures to assist in the recognition and exclusion of Addison's disease: A preliminary report. *Proc. Staff Meet., Mayo Clin.* 16: 577. 1941.
8. Fraser, R., F. Albright, and P. H. Smith: The value of the glucose tolerance test, the insulin tolerance test and the glucose-insulin tolerance test in the diagnosis of endocrinologic disorders of glucose metabolism. *J. Clinical Endocrinology* 1: 297. 1941.
9. Means, J. H., S. Hertz and J. Lerman: The pituitary type of myxedema or Simmonds' disease masquerading as myxedema. *Tr. Assn. Am. Phys.* 55: 32. 1940.
10. Lerman, J., and H. D. Stebbins: The pituitary type of myxedema. *J. Am. Med. Assoc.* 119: 391. 1942.
11. Byrom, F. B.: The nature of myxedema. *Clin. Sc.* 1: 273. 1934.
12. Williams, R. H., and J. L. Whittenberger: Unpublished data.
13. Thorn, G. W., and L. L. Engel: Effect of sex hormones on renal excretion of electrolytes. *J. Exper. Med.* 68: 297. 1938.
14. Thorn, G. W., and K. Emerson, Jr.: Rôle of gonadal and adrenal cortical hormones in production of edema. *Ann. Int. Med.* 14: 757. 1940.
15. Kenyon, A. T., I. Sandiford, A. H. Bryan, K. Knowlton and F. C. Koch: The effect of testosterone propionate on nitrogen, electrolyte, water and energy metabolism in eunuchoidism. *Endocrinology* 23: 135. 1938.
16. Kochakian, C. D., and J. R. Murlin: Relationship of synthetic male hormone, androstendion, to protein and energy metabolism of castrate dogs, and protein metabolism of normal dog. *Am. J. Physiol.* 117: 642. 1936.
17. Kochakian, C. D.: Testosterone and testosterone acetate and protein and energy metabolism of castrate dogs. *Endocrinology* 21: 750. 1937.
18. Papanicolaou, G. N., and E. A. Falk: General muscular hypertrophy induced by androgenic hormone. *Science* 87: 238. 1938.
19. McCullagh, E. P., and H. R. Rossmiller: Methyl testosterone; calorigenic activity. *J. Clinical Endocrinology* 1: 503. 1941.
20. Thorn, G. W., G. F. Koepf, R. A. Lewis and E. F. Olsen: Carbohydrate metabolism in Addison's disease. *J. Clinical Investigation* 19: 813. 1940.

Experimental Modification of Water and Salt Output in Patients with Diabetes Insipidus

[Diabetes Insipidus]

THOMAS H. MCGAVACK, M.D.,
LINN J. BOYD, M.D. AND
PHILLIP GELVIN, M.D.

From the Department of Medicine, New York Medical College, and the Medical Services of Flower and Fifth Avenue Hospital and Metropolitan Hospital, New York City

LARGELY THROUGH the work of Ranson and his associates (1), inability of the kidney tubule to resorb water in normal quantity has been established as the primary functional disturbance in the patient suffering from the syndrome of diabetes insipidus. Because of the large volume of urine thus secreted, such subjects seem peculiarly adapted to a study of the action of hormones and other agents which are apparently capable of affecting water and electrolyte balance in the body.

Three patients with diabetes insipidus, two of the persistent and one of the intermittent type, have served as the basis of the study. In each of these three patients the presence of diabetes insipidus has been proven by the use of water-deprivation and salt-loading tests when the patients have been successively on a dietary of average, low, and high salt content, respectively.

METHODS AND PROCEDURE

Each of the three patients with proven diabetes insipidus was hospitalized for several weeks prior to a study of the influence of various factors upon the output, concentration and sodium and chloride content of the urine. During this preliminary period of study, which in no instance lasted less than 10 days, the patient was placed upon a diet, the carbohydrate, protein, fat, sodium, potassium, and chloride content of which was known. This diet was continued throughout the experimental period, except when alterations were necessary in the content of sodium chloride for the performance of water and salt-loading and deprivation tests.

Received for publication July 27, 1942.
Read at the twenty-sixth annual meeting of the Association for the Study of Internal Secretions at Atlantic City, N. J., June 9, 1942.

In figures 1 and 2, the results of the tests are given in the order in which they were performed, and the number of days each regime was utilized is recorded in parentheses beneath the caption 'period.' Between each period of experimentation not less than one week was allowed to elapse before beginning the next one. In the case of the estrogen, α-estradiol dipropionate, a period of at least two weeks elapsed following the last injection. After desoxycorticosterone

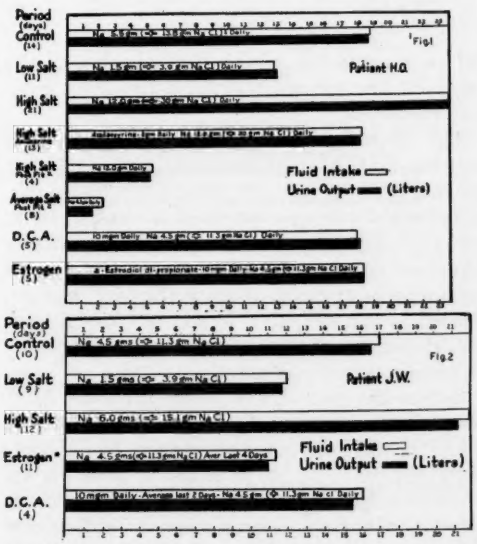

Fig. 1. INFLUENCE OF VARIOUS FACTORS ON FLUID INTAKE AND URINARY OUTPUT IN DIABETES INSIPIDUS, *patient H. O.* 1. Ward diet with known Na content used throughout all periods of observation. 2. One cc. of pitressin tannate in oil daily. Fig. 2. INFLUENCE OF VARIOUS FACTORS ON FLUID INTAKE AND URINARY OUTPUT IN DIABETES INSIPIDUS, *patient J. W.* Daily diet throughout contained approximately C., 350 gm. P., 100 gm.; F., 110 gm.; calories 2790. α-Estradiol dipropionate, 10 mg. (=60,000 I.U.) daily.

acetate, no other medication was used until 10 days following the last dose.

Patients were allowed the freedom of the wards throughout the experimental period, so that a reasonably normal activity level could be maintained. However, fluid intake and output were carefully measured by a triple check, the patient, the ward attendant and the nurse each making separate measurements before discarding the specimen. Care was taken that diet from an extraneous source was not used. Inasmuch as 2 of these patients, upon whom most of the studies were performed, were desirous of working and yet were unable to keep a job because of the polydipsia and polyuria, there was little or no tendency to cheating.

The determination of sodium in the blood and urine was made by the method of Darnell and Walker (2); that of potassium in the same fluids, by the procedure of Drekter (3), in which silver cobaltic nitrate instead of cobaltic nitrate is used as a precipitating agent, and colorimetric estimation is substituted for permanganate titration. Urinary chlorides were estimated by the method of Wilson and Ball (4) with special care for the preservation and periodic restandardization of reagents.

Salt-loading tests were performed as follows. After the patient had been on the standard diet for at least 3 days, he was given in lieu of breakfast, on the morning of the test, 0.25 gm. of sodium chloride per kg. of body weight as a 10 per cent aqueous solution. Blood and urinary determinations of sodium and chloride were performed just before beginning the test and at hourly intervals up to 5 hours following the ingestion of salt.

Fluid intake and urinary output were carefully measured. As a result of previous investigation, dietary water was found to vary little, and thus was the patient was placed on a regime of water restriction. Results are recorded in table 1. In all patients following a low-salt regime, the test period of 24 hours could be completed, but not without distressing symptoms.

Six hours after restricting the intake of water in patient C. A., who for several days previously had utilized a diet high in salt, symptoms of shock occurred which were sufficiently severe to necessitate stopping the test. At the patient's request, a similar 6-hour period of water deprivation was used after a low-salt intake, at the end of which time the patient was very uncomfortable and was apprehensive lest he feel as distressed as on the preceding occasion. Patients C.A. and J.W. showed a severe water deficit with urinary output far in excess of fluid intake (table 1). The primacy of the polyuria coupled with the behavior following the administration of a single large dose of salt definitely places these cases in the category of the syndrome of diabetes insipidus commonly seen.

The third case, H.O., responded to reduced fluid intake by a markedly reduced urinary volume not greatly beyond that of the fluid intake. A rise in temperature, profuse sweating, nausea, vomiting, and severe abdominal pain were induced as the fluid restriction was continued. The test was repeated sev-

not determined in the present series of observations. Respiratory and fecal water and the water of insensible respiration were not estimated, but were believed to be reasonably constant throughout the period of study, as none of the patients suffered from diarrhea nor had any evidence of unusual sweating from activity during the experiment.

RESULTS

Water-restriction tests. At the end of periods of low-salt intake (1.5 to 3.9 gm. daily) and normal or high-salt feeding (12 to 30 gm. daily), respectively,

TABLE 1. EFFECTS OF VOLUNTARY RESTRICTION OF FLUID INTAKE ON URINARY OUTPUT AFTER LOW AND HIGH NORMAL SODIUM CHLORIDE FEEDING

Patient	Approximate Daily Intake of Sodium Chloride		Test Period (hr.)	Fluid Intake, cc.	Urine Output, cc.	Comment
	No. days prior to test	Amount gm.				
J.W.	8	3.5	24	1500	7000	Headache toward end of period
J.W.	13	15.0	9	1500	8550	Severe headache, faintness; temp. 101° F. Immediately after test ended drank 2500 cc. water
C.A.	3	1.5	6	750	1700	Drank 700 cc. water at end of test period
C.A.	3	12.0	6	740	2400	Thirst intense; bolted out of bed to drink 1680 cc. water
H.O.	12	3.9	24	2520	3550	Increased temp., sweating, nausea, vomiting, abdominal pain

TABLE 2. EFFECTS OF ADMINISTERING 0.25 GM. OF NaCl IN A 10 PER CENT AQUEOUS SOLUTION PER KILOGRAM OF BODY WEIGHT

Subject	Hourly Determinations of																	
	Blood serum chloride as NaCl; mg. per 100 cc.						Urinary											
							Chloride as NaCl; mg. per min.						Output, cc. per min.					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Normal	570		620	655		580	6.0	7.2	10.3	18.2	9.0	9.0	1.0	1.2	1.7	2.4	1.8	1.0
C.A.	590	620		635		600	2.1	1.8	2.4	2.0	2.5	2.4	11.2	8.0	10.0	12.2	15.1	17.0
J.W.	555	600	610	600	560		2.0	2.0	3.1	3.0	2.9	2.7	12.0	13.0	16.1	19.2	20.0	22.1
H.O.	580	610	630	605	575	540	2.0	4.0	4.1	4.8	4.2	3.3	18.1	22.0	17.3	16.4	22.7	18.0

eral times, each time with similar results, the temperature sometimes rising to 102° F. After 'salt loading,' the polyuria was more marked, but still not profound. We have classified this patient as a 'primary thirst' type of diabetes insipidus.

Salt-loading tests. Results of these tests for C.A. have been described in detail in a previous report (5). Results of the tests in all of the patients are compared with the normal response in table 2. As contrasted with the normal response, the significant findings in all patients were *a*), a normal range for serum chlorides; *b*), and inability to concentrate salt in the urine; and *c*), a further increment in the already increased output of urine per minute.

The results of the influence of low and high salt intake, estrogens, desoxycorticosterone acetate, and amidopyrine upon fluid balance in *H.O.* and *J.W.* are summarized in figures 1 and 2, and tables 3 and 4. Data for C.A. are contained in a previous report (5) and agree in all particulars with the findings in patient *J.W.*

Low-salt feeding. If the diet was changed from one containing 11.3 gm. of sodium chloride (average dietary intake) to one containing approximately 3.9 gm. of sodium chloride, there was an overall reduction in urinary volume of approximately 30 per cent. The time necessary for maximum effect varied from individual to individual but was usually apparent in from 3 to 7 days (fig. 3).

High-salt feeding. In patient *H.O.*, 30 gm. of salt was used daily with an increase of approximately 25 per cent in the urinary output, a moderate rise in the specific gravity, and a two-fold increment in the concentration of chloride. *J.W.* responded to half of this amount of sodium chloride with almost a 30 per cent rise in urinary volume, a very slight, perhaps insignificant, rise in specific gravity, and a 25 per cent elevation in the concentration of chloride.

α-Estradiol dipropionate. In patient *J.W.*, following the daily use of 10 mg. of α-estradiol dipropionate,[1] there was a definite reduction in urinary output, slightly greater than that seen from a regime of low-salt feeding. This, however, was not in evidence until the 4th day of treatment and did not reach its maximum until the 9th day (fig. 4). Concomitantly there was a slight rise in specific gravity, no appreciable effect upon urinary chloride concentration, and a marked positive balance in chloride metabolism with increase in weight.

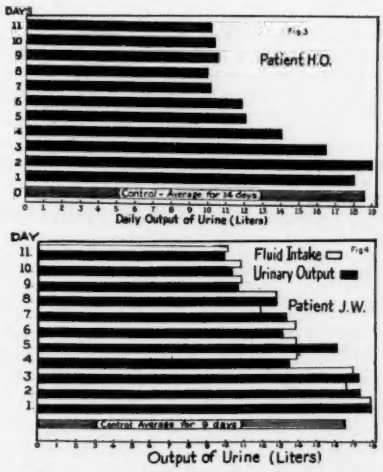

Fig. 3. INFLUENCE OF LOW SALT INTAKE ON URINARY OUTPUT IN DIABETES INSIPIDUS. The diet contained 1.5 gm. of Na (=3.9 gm. of NaCl). Fig. 4. INFLUENCE OF ESTROGENS ON FLUID INTAKE AND URINARY OUTPUT IN DIABETES INSIPIDUS. Diet contained 4.5 gm. of Na (as NaCl=11.3 gm.). α-Estradiol dipropionate, 10 mg. daily dosage.

In patient *H.O.*, during a 5-day period, the estrogen in daily doses of 10 mg. had no appreciable effect upon either the volume of urine or the concentration of the urinary chlorides. There was, however, significant retention of sodium chloride.

The influence of estrogens upon patient C.A. was not studied.

As a result of clearance tests[2] it was shown that the estrogen did not affect glomerular filtration appreciably, but that it did materially increase tubular

[1] The α-estradiol dipropionate and desoxycorticosterone acetate were supplied through the courtesy of Dr. Max Gilbert, of the Schering Corp., Bloomfield, N. J.

[2] We are indebted to Dr. H. Elias for inulin clearance tests made in connection with this and one other case.

TABLE 3. URINARY VOLUME, CONCENTRATION AND CHLORIDES IN DIABETES INSIPIDUS UNDER VARIED CONDITIONS, PATIENT *H.O.*

Regime	Highest Specific Gravity	Averaged 24-hour			Urinary Concentration of Cl, % as NaCl	Pody Weight, lb.
		Urinary output, l.	Total Cl (as NaCl)			
			Intake, gm.	Output, gm.		
Control	1.005	18.6	11.3	11.2	0.060	160
Low salt	1.006	12.9	3.9	3.8	0.029	161
High salt	1.006	23.3	30.1	29.8	0.127	164
High salt and amidopyrine[1]	(a) 1.008 (b) 1.008	18.2 19.1	30.1 30.1	36.6 31.9	0.201 0.166	163 163
High salt and pitressin[2] (c)	1.017	5.1	30.1	30.4	0.596	162
Average salt and pitressin[2]	1.015	1.6	11.3	11.3	0.706	167
D.C.A.[3]	1.004	18.2	11.3	11.4	0.062	167
After D.C.A.[4]	1.006	17.1	11.3	15.2	0.089	164
Estrogen[5]	1.006	18.4	11.3	9.7	0.052	166

Each figure represents an average of from 2 to 5 determinations, none of which was made until the treatment indicated had been employed for at least 3 days. Control periods between each 2 test periods of not less than 5 days each were utilized.

[1] 2 gm. daily; (a) 1st and 2nd days; (b), 12th and 14th days.
[2] Pitressin tannate in oil, 1 cc. daily. (c), 1 determination, 4th day.
[3] 10 mg. daily.
[4] First day after desoxycorticosterone acetate discontinued.
[5] α-Estradiol dipropionate, 10 mg. daily.

resorption of salt and, in one instance, of water as well.

That the dosages used in these studies are not physiologic is evidenced by the fact that, after having received the estrogen for 7 or 8 days, patient *J.W.*, a strong, virile type of mulatto, complained of

TABLE 4. URINARY VOLUME, CONCENTRATION AND CHLORIDES IN DIABETES INSIPIDUS UNDER VARIED CONDITIONS, PATIENT *J. W.*

Regime	Highest Specific Gravity	Averaged 24-hour			Urinary Concentration of Cl, % as NaCl	Body Weight, lb.
		Urinary output, l.	Total Cl, as NaCl			
			Intake, gm.	Output, gm.		
Control	1.002	16.5	11.3	11.0	0.065	163.0
Low salt	1.003	11.7	3.9	4.1	0.035	163.5
High salt	1.004	21.3	15.0	15.2	0.080	162.5
Estrogen[1]	1.004	10.0	11.3	7.8	0.070	168.5
High salt and pitressin[2]	1.012	5.3	30.0	28.7	0.540	162.5
Average salt and pitressin[2]	1.013	2.7	13.8	14.0	0.510	164.0
High salt and amidopyrine[3]	1.009	18.2	30.0	30.3	0.166	163.0
D.C.A.[4]	1.003	15.4	11.3	9.8	0.063	167.0
After D.C.A.[5]	1.004	14.0	11.3	17.8	0.127	165.0

Each figure represents an average of from 2 to 5 determinations, none of which was made until the treatment indicated had been employed for at least 3 days. Control periods between each two test periods of not less than 5 days each were utilized.

[1] α-Estradiol dipropionate, 10 mg. daily.
[2] Pitressin tannate in oil, 1 cc. daily.
[3] 2 gm. daily.
[4] 10 mg. daily.
[5] Second day after desoxycorticosterone acetate discontinued.

diminution in power of erection and in sex desire, associated with which there appeared a sensitiveness of the breasts with slight intensification of the pigmentation and feminization of the secondary mammary areolae.

Desoxycorticosterone acetate. As a result of the daily administration of 10 mg. of desoxycorticosterone acetate[1] to patients *J.W.* and *H.O.* for periods of 4 and 5 days, respectively, there was no alteration of the fluid exchange. However, some retention of sodium chloride occurred, which was rather promptly released in the period following treatment. This was more striking in the case of *J.W.* than in that of *H.O.* and was thought to be related to the difference in the type of diabetes insipidus present in each instance. Chloride and inulin clearance tests showed that, in the dosages used, desoxycorticosterone acetate caused a marked increase in the tubular resorption of sodium and chloride, which was compensated for as soon as the effect of the drug began to decline.

CASE REPORTS

Case 1, C.A.,[3] a 30-year-old white male, developed polyuria (up to 28,000 cc. daily) and polydipsia at the age of 18 shortly after recovering from a post-pneumonic encephalitis. At the age of 26 he was given intensive antisyphilitic treatment. During the period of the present observations he was suffering from advanced pulmonary tuberculosis, which eventually resulted fatally.

The anatomical diagnoses made following postmortem examination were: bilateral caseous ulcerative tuberculosis of the lungs, to which death was attributed; amyloidosis of the liver, spleen, and kidneys; tuberculous ulceration of the small and large intestines; degeneration of the supraoptic nucleus and of the posterior lobe of the pituitary gland, in association with diabetes insipidus.

Case 2, *H.O.*, a white male now 20 years old, has been under observation since the age of 16, at which time he was admitted to the hospital complaining of pain in the lower right quadrant of the abdomen so severe in nature that appendectomy was performed for a relatively normal appendix. During the post-operative course, the fluid intake and output averaged approximately 24 liters daily. He stated that polyuria and polydipsia had been present since the age of 2 years. There was an average nocturia of 6 and a diuria of 25 times, because of which it had been impossible for him to retain a position of any sort. If he attempted to decrease his intake of water, severe abdominal pain invariably ensued which had led to hospitalization on several occasions. He has never had any trauma to the skull; birth was normal and without instruments. He had rickets, measles, mumps, chicken pox, and whooping cough in childhood. Tonsillectomy and adenoidectomy were performed at the age of 4. For most of his life he has suffered from generalized headaches recurring periodically every 3 to 4 days and unrelated in any way to food or water intake or to time of day. At times his vision has been blurred, and he has found that he 'cannot see things to the side.' He has had no attacks of complete blindness, convulsions, unconsciousness, or motor or sensory loss. He has never experienced any olfactory, auditory, gustatory or visual hallucinations.

On physical examination, one observed an undersized individual of unusual appearance. The frontal bosses were prominent, the eyelids were puffy and slanted in a Mongolian-like fashion, and the eyeballs were prominent. There was a divergent squint, despite which the interpupillary distance was disproportionately small. There was a short, saddle-type nose; the lower jaw protruded slightly; the lips were thick, and labial speech was disturbed. His weight was 147 lb.; height, span, and lower measurement, 60, 61, and 30.5 inches, respectively. The distribution of fat pads suggested that of a Fröhlich's syndrome, although all other features, such as sex organs, hair distribution, and other secondary sex characteristics were normal. The neck was short, thick, and full. The heart and lungs were negative; the blood pressure was 116 and 70 mm. Hg systolic and diastolic, respectively. Rectal examination revealed a prostate of normal size. All reflexes were bilaterally symmetrical and equal; no pathologic reflexes could be elicited.

Since many of the laboratory tests performed in connection with this case have been repeated frequently without material alteration through the years, the results of a few representative analyses follow. The blood Wassermann reaction was negative. Routine urinalysis was negative save for the low specific gravity and the large volume. Blood plasma proteins in percentage were: albumin, 4.1; globulin, 2.1; and fibrinogen, 0.32; total, 6.52. Other blood chemical constituents in mg. per cent were: urea nitrogen, 9.0; creatinine, 0.8; sugar, 75; chlorides (as NaCl) 553, rising slightly in response to salt-loading tests, but returning to normal within 6 hours; total lipids, 868; free fatty acids, 52; neutral fats, 310; total cholesterol, 202; free cholesterol, 56; esters, as cholesterol oleate, 247; lipid phosphorus, 8.6; and phospholipids, 203. The blood count was normal. The red cells sedimented 2 mm. in 15 minutes, and 10 mm. in one hour. Blood sugars at hourly intervals following the oral ingestion of 100 gm. of glucose were, in mg. per cent, 67, 94, 92, 75 and 70 respectively. The spinal fluid was clear; it was under no increase in pressure, showed a total protein of 24 mg. per cent with no increase in globulin; chlorides, as NaCl, 692 mg. per cent; and colloidal gold curves were unmodified. The basal metabolic rate was −12. The electrocardiographic tracing was normal throughout. The Wassermann reaction was negative.

A gastro-intestinal roentgenographic series revealed no pathology. Roentgenograms of the skull showed a sella turcica of relatively small proportions as compared with the size of the cranial cavity; the posterior clinoid processes were unusually thick and erect. The sphenoidal sinus was poorly developed.

On ventriculography and encephalography, no abnormality of the ventricular system could be made out, although the neuro-surgeon made a note to the effect that the pia arachnoid was somewhat thickened and, in the absence of pressure signs, interpreted this as the result of an old meningoencephalitis.

[3] Findings in this case have been reported in detail elsewhere (see reference 5).

Periods of tubular vision have alternated with normal vision. Revised Stanford-Binet intelligence tests revealed a mental age of approximately 13 years.

Comment. The patient states that there have been spontaneous remissions, lasting as long as several weeks, in the polyuria and polydipsia with a urinary output not exceeding 3,000 cc. daily on some occasions. However, such changes have not been present during hospitalization except following encephalography, after which the output decreased for a few days to about 3,500 cc.

Final diagnosis. Diabetes insipidus and mental and physical retardation secondary to an old meningoencephalitis.

Case 3, *J.W.*, a 39-year-old male mulatto, has suffered from polydipsia, polyuria, and pollakiuria for as long as he can remember. He stated that he had been accustomed to pass about 5 gallons or urine every 24 hours, and that continuous water drinking and urgency to urinate had forced him to give up or caused him to be discharged from a number of positions he could otherwise have held without difficulty. He recalled having had severe febrile attacks each fall for 3 successive seasons during childhood. His birth was normal; and teething, walking, and talking were all accomplished at the usual ages. There were no other significant facts in his own past history or in his family history.

Physical examination revealed a well-developed, well-nourished, muscular individual, 71 inches tall and weighing 162 lb. His physical examination was essentially negative. The blood pressure was 132 and 82 mm. Hg systolic and diastolic, respectively. The eyegrounds were normal; all reflexes were normal and no pathological ones were present. Laboratory studies made at or near the time of admission led, with the exception of the urine, to normal findings. The electrocardiogram was normal. Roentgen-ray examinations of the chest, skull, and pelvis revealed no pathologic changes. Repeated routine urine analyses showed nothing abnormal save a specific gravity routinely below 1.003. The blood Wassermann reaction was negative. The blood count showed a hemoglobin of 81 per cent, a red cell count of 4.8 million per cu. mm., a white cell count of 8.4 thousand per cu. mm., and a differential count (in per cent) of polymorphonuclear neutrophiles, 72; lymphocytes, 24; and eosinophiles 4. The basal metabolic rate was −6. Blood proteins in per cent were: albumin, 4.34; globulin, 2.91; total, 7.47. Other blood chemical constituents, in mg. per cent, were: urea nitrogen, 10; creatinine, 0.9; sugar, 90; chlorides (as NaCl), 575; sodium, 332.9; potassium, 18.6; total cholesterol, 176; and cholesterol esters, 118.

His course in the hospital was uneventful except for variations in water and salt balance and can best be followed by study of figures 2 and 4, and tables 1, 2 and 4.

Final diagnosis. Diabetes insipidus of undetermined etiology, possibly familial in type.

DISCUSSION

Types of diabetes insipidus. Perhaps by definition we should confine the use of the term diabetes insipidus to that type of polyuria and polydipsia associated with a depressed or destroyed function of the supraoptico-hypophyseal tract and the posterior pituitary, as a result of which posterior pituitary secretion is lessened or stopped, and the kidney loses much of its regulatory power over the resorption of water from the tubules. With such a definition, the primacy of the polyuria among the symptoms of the disease cannot be denied, and has been amply proven by Ranson and his associates (1), who have critically reviewed the literature.

The type of polyuria seen in one of the patients (*H.O.*) described above would have no place in such a definition of the disease. Yet, except for water-deprivation tests, polyuria in this case reacted similarly to that of the patients with the classical syndrome. The prompt response to posterior pituitary substance would appear to preclude the condition being of the hysterical type of polydipsia and polyuria. That such responses were not psychic was demonstrated by the fact that no other treatment gave him as much relief or caused such good concentration of the urine as did the posterior pituitary substance. Moreover, saline injections were given in the place of the pitressin, with the same technique and psychological management. Despite this fact, urinary volume rose, and the specific gravity and urinary concentration of chlorides decreased.

As can be seen from his history, this patient had periods of relative freedom from the condition, rather than the permanent polyuria of the more classical type. Similar cases have been previously described in human beings (6) and in dogs (7). Experimentally, the existence of a thirst-primacy type of diabetes insipidus has always been open to question (1). While Curtis' (8) view that all diabetes insipidus can be looked upon as a 'hypothalamic thirst phenomenon' is untenable, it does, however, appear that not one but a number of factors influence the character and clinical behavior of the syndrome known as diabetes insipidus. We should not, therefore, overlook disturbances in water balance which may fail to conform to a single rigid pattern (9). This is particularly worthy of emphasis at a time when thyroid substance (1, 10), pancreatic (11), adrenal, and renal extracts, vitamins (12), and other materials of equally diverse origin have been shown to exert an effect upon fluid exchange within the body.

Influence of sodium chloride. Urinary output could be lowered or raised at will in all 3 of our patients by a reduction or increase, respectively, in the amount of salt ingested. This variation was directly propor-

tional to the amount of salt in the diet, but was not of straight-line magnitude. In response to these changes, sodium and chloride balance was maintained not only by an increase or decrease in the quantity of the urine, but also by a variation in the amount of tubular re-absorption. It would appear that salt itself is capable of increasing the ability of the renal tubules to resorb water. It must be remembered that no case of human diabetes insipidus has ever been recorded in which this function was entirely lost (1, 13, 14). For this reason, it may be possible that salt exerts its effect not upon the kidney tubule directly but upon the remaining function of the supra-optico-hypophyseal system through which the antidiuretic hormone is produced. Both Peters (15) and Fisher and his associates (1) emphasize the primary effect of this hormone on the re-absorption of water from the kidney tubule and stress the fact that this action is out of all proportion to its influence upon the excretion of solutes. On the other hand, in our patient C.A., no trace of intact fibers within the supra-optico-hypophyseal tract could be found, and atrophy of the cells of the posterior pituitary was striking. Nevertheless, the power to produce some concentration of the urine was not entirely lost. These observations suggest a certain degree of autonomous action on the part of the kidney itself.

From the present studies, we are justified only in emphasizing the stimulating effect of salt upon the tubular resorptive power of the kidney, for the higher the concentration of salt, the better the tubule succeeded in its effort to resorb water.

Influence of estrogen. In connection with our observations, it would appear that the human being with diabetes insipidus responds to large dosages of an estrogen in much the same manner as does a normal person. Thorn (16, 17) has noted a retention of body fluid and electrolyte in the normal individual under the influence of follicular hormone. Some workers do not agree with this conclusion, but the differences of opinion on this subject may be related to the fact, emphasized by Thorn himself, that the action is temporary and cannot be maintained even by the continued administration of the hormone. During the period of observation in the present studies (up to 11 days), the patients remained in a phase of positive sodium and chloride balance. Because of the prolonged action of the α-estradiol dipropionate the reversion to normal was gradual, and could not be closely followed by the methods at hand. In view of the unpleasant reaction in one patient and the failure to reduce urinary volume appreciably even with large doses, the hormone possesses little if any therapeutic value in a disease like diabetes insipidus. However, its positive influence upon water and salt balance has been well demonstrated in our cases.

Such a statement justifies more than passing comment, as the rôle of the estrogens in disturbing the water and salt distribution in menstruating women has been as frequently denied as confirmed. This is the first study of the effects of the estrogens in a disease in which variations in electrolyte and fluid equilibrium are unusually easy to follow. It would appear that many authorities have unnecessarily minimized the ability of follicular hormone to create a positive balance in the body for both water and salt.

Influence of desoxycorticosterone acetate. In view of the now well-known ability of desoxycorticosterone acetate to produce a syndrome not unlike that of diabetes insipidus (7, 18–23) it was rather surprising to find in the literature no report of the study of the hypothalamic region in such animals. Almost equally strange was the absence of any investigation of the influence of desoxycorticosterone acetate upon the already-established diabetes insipidus of lower animals and man.

The frequently observed diuresis associated with the administration of large doses of desoxycorticosterone acetate and a high salt intake in laboratory animals has been studied critically by Mulinos and his associates (18) in an effort to establish a relationship between it and diabetes insipidus. In the experience of these workers, salt-loading and restriction, and water-loading and deprivation tests have resulted in changes that are comparable in every respect to the alterations in water and salt metabolism which are seen in animals with diabetes insipidus. Their work suggests that the syndrome of diabetes insipidus may arise either from a specific destructive lesion of the hypothalamic and posterior hypophyseal regions, or from an overactivity of certain functions of the adrenal cortex. In further proof of the correctness of this view stands the evidence that adrenalectomy has improved the diuresis of animals with diabetes insipidus (24–27).

On the basis of these facts, one would have expected the use of desoxycorticosterone acetate in our patients to be accompanied by a further increase in urinary volume in an effort to eliminate the retained sodium. This was not the case, despite the fact that the retention of sodium as a result of administration of desoxycorticosterone acetate was easily demonstrated, and its rapid elimination observed as soon as the drug action was spent. Our periods of observation may have been too short for development of the diabetes insipidus-like effects, for it seems to be well established that, during the earliest days of administration to dogs, a retention of chloride without appreciable diuresis may occur (18). Moreover, the dose of

desoxycorticosterone acetate may have been too small to elicit the polyuric and saline diuretic actions, but it seemed to be the largest dose compatible with safety in the human being on the basis of previous studies in patients with Addison's disease (28).

It may be argued that the increased excretion of chloride and sodium obtained after discontinuing desoxycorticosterone acetate in our patients was due to the saline diuresis it may produce. On the contrary, this increase in urinary chloride was associated with no change or, indeed, with a slight decrease rather than an increase, in urinary volume.

The diuresis of diabetes insipidus and that of desoxycorticosterone acetate intoxication seem to differ in yet another way. With the diuresis of desoxycorticosterone acetate, the blood serum sodium usually rises, whereas in diabetes insipidus it is apparently never elevated. The significance of this difference is not apparent and may be a matter of degree only, or, on the other hand, a function of time. Most of the observations on serum sodium levels in diabetes insipidus have been made after the disease had been present for considerable periods of time, i.e., after the body had had an opportunity to adjust sodium and chloride balance by the excretion of large quantities of urine of a low specific gravity; whereas in the majority of the studies of desoxycorticosterone acetate intoxication, the interval of observation has been short and the long-continued influence of the drug on electrolyte balance has received little or no attention. It is our experience that the high levels of blood sodium seen in cases of Addison's disease under treatment with high dosage of desoxycorticosterone acetate give way sooner or later to more normal or entirely normal values, even if the intake of sodium is varied. This would suggest that, if sufficient time is allowed, the chloride balance in desoxycorticosterone acetate poisoning may behave in a manner not unlike that seen in the animal with diabetes insipidus.

SUMMARY

1. The clinical findings in three cases of diabetes insipidus are summarized.

2. Changes in the volume, concentration, and sodium and chloride content of the urine under a variety of influences, including low and high salt intake, posterior pituitary substance, amidopryine, follicular hormone, and desoxycorticosterone acetate, have been detailed.

3. Low salt intake decreases the urinary volume and lowers the chloride concentration. High salt intake increases the volume as well as the concentration.

4. In two patients, water deprivation was attended by a relative failure to check urinary output, whereas in the third patient, it was reduced nearly to the level of water intake.

5. Estrogen caused a retention of sodium and chloride in all patients and an appreciable reduction in the volume of urine, but made no change in its specific gravity.

6. Desoxycorticosterone acetate produced a positive sodium and chloride balance but did not materially influence the volume of the urine in any of the three patients. The retention of salt was accompanied by a rapid gain in weight and was followed temporarily by a marked negative balance of sodium and chloride.

7. Amidopyrine in the dosages used raised the specific gravity and the chloride concentration of the urine, but had little or no influence upon the total chloride excretion.

8. Posterior pituitary substance exerted its characteristic anti-diuretic effects in each patient. This was true irrespective of whether each was receiving a high, average, or low salt intake, although the urinary volume was least whenever a low sodium chloride intake was employed.

CONCLUSIONS

The primary disturbance following a deficiency in the secretion of the posterior lobe of the pituitary gland occurs in the kidney tubules and appears to be either *a*), a failure in the preferential re-absorption of water, or *b*), a too-avid resorption of salt, or *c*), both.

The water-resorptive power of the tubule is decreased by low salt intake, and increased by high salt intake, amodipyrine, posterior pituitary substances, and estrogens.

The salt-resorptive power of the tubule is increased by estrogens and desoxycorticosterone acetate, and decreased temporarily by desoxycorticosterone acetate in the phase following treatment.

REFERENCES

1. Fisher, C., W. R. Ingram and S. W. Ranson: Diabetes Insipidus and the Neuro-hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-hypophyseal System. Edwards Brothers, Inc., Ann Arbor, Michigan. 1938.
2. Darnell, M. C., Jr., and B. S. Walker: Determination of sodium in biological fluids. *Indust. & Engin. Chem., Anal. Ed.* 12: 242. 1940.
3. Drekter, I. J.: In press.
4. Wilson, D. W., and E. G. Ball: A study of the estimation of chloride in blood and serum. *J. Biol. Chem.* 79: 221. 1928.
5. McGavack, T. H., J. W. Benjamin and S. Liebowitz: Diabetes insipidus. *Arch. Neurol. & Psychiat.* 44: 867. 1940.
6. Rutherford, R. B., and J. Q. Griffith: Pitressin-inhibiting substance in the serum of a patient with transient diabetes insipidus. (Soc. proc.). *Arch. Neurol. & Psychiat.* 47: 188. 1942.
7. Ragan, C., and others: A syndrome of polydipsia and polyuria induced in normal animals by desoxycorticosterone acetate. *Am. J. Physiol.* 131: 73. 1940.
8. Curtis, G. M.: The production of experimental diabetes insipidus. *Arch. Int. Med.* 34: 801. 1924.

9. WALKER, A. M.: Experiments upon the relation between the pituitary gland and water diuresis. *Am. J. Physiol.* 127: 519. 1939.
10. BLOTNER, H., AND E. C. CUTLER: Total thyroidectomy in the treatment of diabetes insipidus. *J. Am. Med. Assoc.* 116: 2739. 1941.
11. BARNES, B. O., J. F. REGAN AND J. G. BUENO: Is there a specific diuretic hormone in the anterior pituitary? *Am. J. Physiol.* 105: 559. 1933.
12. SMITH, S. G.: Red staining of paws and whiskers as in vitamin B_2-complex deficient rats after dehydration. *Proc. Soc. Exper. Biol. & Med.* 49: 691. 1942.
13. KENNAWAY, E. L., AND J. C. MOTTRAM: Observations upon two cases of diabetes insipidus; with an account of the literature relating to an association between the pituitary gland and this disease. *Quart. J. Med.* 12: 225. 1919.
14. FORSCHBACH, AND WEBER: Beobachtungen uber die Harn- und Salz-Ausscheidung im Diabetes insipidus. *Ztschr. f. klin. Med.* 73: 221. 1911.
15. PETERS, J. P.: Body water: The exchange of fluids in man. Charles C Thomas, Springfield, Ill., 1935.
16. THORN, G. W., K. R. NELSON AND D. W. THORN: A study of the mechanism of edema associated with menstruation. *Endocrinology* 22: 155. 1938.
17. THORN, G. W., AND L. L. ENGEL: The effect of sex hormones on the renal excretion of electrolytes. *J. Exper. Med.* 68: 299. 1938.
18. MULINOS, M. G., C. L. SPINGARN AND M. E. LOJKIN: A diabetes insipidus-like condition produced by small doses of desoxycorticosterone acetate in dogs. *Am. J. Physiol.* 135: 102. 1941.
19. SILVETTE, H., AND S. W. BRITTON: A theory of cortico-adrenal and post-pituitary influence on the kidney. *Science* 88: 150. 1938.
20. COREY, E. L., H. SILVETTE AND S. W. BRITTON: Hypophyseal and adrenal influence on renal function in the rat. *Am. J. Physiol.* 125: 644. 1939.
21. KUHLMANN, D., AND OTHERS: Toxic effects of desoxycorticosterone esters in dogs. *Science* 90: 496. 1939.
22. SELYE, H., AND L. BASSET: Effect of desoxycorticosterone and testosterone on water and chloride metabolism. *Proc. Soc. Exper. Biol. & Med.* 45: 272. 1940.
23. COREY, E. L., AND S. W. BRITTON: The antagonistic action of desoxycorticosterone and post-pituitary extract on chloride and water balance. *Am. J. Physiol.* 133: 511. 1941.
24. WINTER, C. A., W. R. INGRAM AND E. G. GROSS: Effect of pitressin injections upon the serum electrolytes and water exchange of cats with diabetes insipidus and adrenal insufficiency. *Am. J. Physiol.* 127: 64. 1939.
25. INGRAM, W. R., AND C. A. WINTER: The effects of adrenalectomy upon the water exchange of cats with diabetes insipidus. *Am. J. Physiol.* 122: 143. 1938.
26. WINTER, C. A., E. G. GROSS AND W. R. INGRAM: Serum sodium, potassium and chloride after suprarenalectomy in cats with diabetes insipidus. *J. Exper. Med.* 67: 251. 1938.
27. INGRAM, W. R., C. A. WINTER AND E. G. GROSS: Observations upon the blood sugar and upon the maintenance of life with persisting polyuria, without cortin, in adrenalectomized cats with diabetes insipidus. *Am. J. Physiol.* 126: 544. 1939.

Use of Testosterone Propionate and Estrogenic Substance in Treatment of Essential Hypertension, Angina Pectoris and Peripheral Vascular Disease

TAYLOR C. WALKER, M.D.

From the Cardiac Clinic of the Beaumont Medical Dispensary, Beaumont, Texas

THE EFFECT of the sex hormones in cardiovascular disease has been the subject of relatively few clinical investigations. In recent medical literature, however, several reports have been published indicating that these substances may find a useful place in the management of certain vascular disorders. In 1939, Edwards, Hamilton and Duntley (1) observed objective and subjective improvement in 7 male patients with organic peripheral vascular disease following treatment with testosterone propionate. All patients presented evidence of major arterial involvement with loss of the popliteal, femoral, and in one case, the iliac pulsations. In 1940, I presented data (2), indicating that the sex hormones gave promise of being effective in the treatment of vascular insufficiency of the coronary, cerebral, and peripheral circulatory systems. Such salutary results were manifested among patients with angina pectoris in an increase of emotional and exercise tolerance, a decrease in the severity of pain, and a general increase in strength. Improvement of the peripheral circulation in patients with occlusive vascular disease was indicated by a return of normal color and temperature, decrease or complete cessation of pain, healing of gangrenous ulcers, increase in exercise tolerance, and an increase in the volume of the peripheral pulse. Subjective evidence of improved cerebral circulation occurred frequently in patients exhibiting clinical syndromes suggesting cerebral circulatory insufficiency.

Since the publication of this study at least three other authors have reported favorable results in the treatment of coronary insufficiency with male hormone. Bonnell, Pritchett, and Rarden (3) observed significant clinical improvement in 22 of 23 patients with angina pectoris and coronary artery disease. Lesser (4) reported excellent results in all patients of a group of 20 men and 4 women exhibiting characteristic angina pectoris. Control patients treated with plain sesame oil did not improve, although subsequently these individuals showed a favorable response to male hormone therapy. The majority of the patients in Lesser's series showed some lowering of the blood pressure during the period of treatment with testosterone propionate. Hamm (5) has recently reported a favorable therapeutic response to male hormone therapy in 7 male patients with unquestionable angina pectoris.

Among European investigators, Steinach and his co-workers (6) observed a fall in systolic blood pressure in 31 of 49 hypertensive individuals treated with androgenic substance. Arndt (7) found testosterone propionate to be therapeutically effective in the treatment of 5 male patients with peripheral vascular disease and 3 male patients with angina pectoris. Greene (8), treating 21 male patients for prostatic hypertrophy with testosterone, observed no significant change in the blood pressure levels of hypertensive individuals in his series. It is not clear to what extent prostatic obstruction and consequent urinary retention were etiologically concerned in the production of hypertension in these patients.

Received for publication July 23, 1942.

CLINICAL MATERIAL AND METHOD OF STUDY

A clinical study of the effect of the sex hormones in cardiovascular disease has been made in the cardiac clinic of the Beaumont Medical Dispensary since January, 1939. Although this study was originally initiated to determine the effect of these substances in essential hypertension, a few patients with angina pectoris and organic vascular disease of the extremities with and without associated hypertension were subsequently included in this investigation. In the course of this study 82 individuals were treated with androgenic and estrogenic substance. Among these patients 56 exhibited primary hypertension; 12 had angina pectoris, and 14 showed physical and symptomatic evidence of organic peripheral vascular disease.

General limitations. In all groups, treatment was limited to ambulatory individuals who were not in

congestive heart failure and who had not suffered a recent coronary occlusion. Sex hormone therapy was further confined to patients who were not obviously ill from any cause other than cardiovascular disease. During the period of treatment with androgenic and estrogenic substance all other general and specific therapeutic measures were suspended. Female patients were treated with standard preparations of estrogenic substance[1] by intramuscular injection. Mixed estrogens and estrone were given in 10,000 I.U. doses; estradiol dipropionate was given in dosages of 0.2 mg. The schedule usually followed was as follows: 4 injections in the first week; 3 injections weekly for the next 4 weeks; 2 injections weekly for the succeeding 4 weeks, and thereafter one injection weekly for 4 more weeks.

Male patients were treated with testosterone propionate[2] by intramuscular injection. In the 1st week 4 doses of 25 mg. each; 2nd week, 3 injections of 25 mg. each; 3rd and 4th weeks, 10 mg. 3 times weekly; 5th through 8th week, 10 mg. twice weekly; 9th through 12th week, 10 mg. weekly.

Hypertension. For the purpose of this study individuals were selected who, on two or more visits to the clinic, presented a consistent elevation of both systolic and diastolic blood pressure levels, and in whom a definite cause for the hyperpiesia could not be ascertained. Hence, patients were excluded who had definite renal lesions, urinary tract obstruction, aortic regurgitation, or any condition definitely known to produce hypertension. Associated arteriosclerosis was not considered an etiologic factor although hypertensive individuals with angina pectoris and/or organic peripheral vascular disease were not included in this group.

Angina pectoris. A diagnosis of angina pectoris was acceptable only when, among other manifestations, a constant, severe, substernal discomfort was routinely precipitated by a given amount of work, and routinely relieved by rest.

Peripheral vascular disease. All patients accepted for study in this group showed loss of the dorsalis pedis, posterior tibial, popliteal, femoral, or iliac pulsation associated with definite signs of impaired peripheral circulation.

Blood Pressure Studies

An analysis of the data in tables 1 and 2 indicates that 81 per cent of the 56 patients showed some lowering of the blood pressure during treatment with the sex hormones. In 33 per cent of all patients the blood pressure showed a significant fall but did not approach a normal level. In 28 per cent the blood pressure returned to, or near, normal figures. The available data on the blood pressure after the cessation of sex hormone therapy indicates that more often than not blood pressures returned to previously high levels, although some lowering of the blood pressure was sustained in a few patients for as long as 6 months after suspension of treatment.

The blood pressure level was not usually affected in patients who demonstrated the higher grades of hypertension associated with symptoms and physical evidence indicating advanced vascular damage. A few patients were exceptions to this observation and the occurrence of transient episodes of marked elevation of blood pressure in this group was definitely reduced. Patients showing a moderate elevation of blood pressure along with symptoms and objective evidence of mild to moderate vascular damage, generally responded more favorably, but the results in this group also were varied. In some instances a return of the blood pressure to, or near, a normal level was affected while in other individuals the blood pressure was not materially changed. There was a rather consistent fall of systolic pressure in those individuals who presented the so-called 'benign' type of hypertension with a high systolic pressure and relatively little elevation of the diastolic pressure. Most of these patients had an associated generalized arteriosclerosis and it is possible that the hypertension in these cases is not etiologically akin to the hyperpiesia among the other patients in this series. Patients presenting evidence of vasospastic or mild hypertension, without vascular damage, routinely responded favorably, a return of the blood pressure to normal being effected in all patients in this group.

Among those patients who demonstrated a fall in blood pressure during sex hormone therapy, it generally appeared that the effect on the blood pressure was inversely proportional to the degree of hypertension, and to the apparent extent of vascular damage. The group of patients who failed to show a significant response includes individuals with no apparent vascular damage as well as some whose symptoms and physical findings denoted widespread structural changes. In other words, when a hypertensive subject was not affected by sex hormone therapy this failure could not always be correlated with the degree of hypertension nor the extent of structural vascular changes.

CASE REPORTS

C. S., a male negro, age 58, complained of severe headaches, dizziness, loss of strength and subjective nervousness. These symptoms had progressively developed during the preceding 6 months. Blood count, Wassermann reaction, basal metabolic rate, and electrocardiographic tracing were within normal limits. The results of urine

[1] The estrogens employed were estradiol dipropionate (Di-Ovocylin), supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.; estrone (Theelin), supplied by Parke, Davis & Co., Detroit, Mich.; mixed estrogens, Reed and Carnick Co.

[2] Testosterone propionate (Perandren) was supplied for this study by Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE ON BLOOD PRESSURE IN MALE PATIENTS WITH ESSENTIAL HYPERTENSION

Case No.	Age, yr.	Race	Treatment and Observation Before Sex Hormone Therapy			Effect of Sex Hormone Therapy on Blood Pressure		Subsequent Observation	
			Time	Treatment	Blood pressure range, mm. Hg	Beginning of treatment, mm. Hg	End of treatment, mm. Hg	Time after sex hormone therapy discontinued	Blood pressure, mm. Hg
1	56	W	1 yr.	Yes	170–165 / 110–100	165 / 100	120 / 85	5 months	130 / 90
2	43	W	1 mo.	No	150 / 90	150 / 90	120 / 80	2 months	125 / 85
3	50	N	2 mo.	Yes	190–170 / 110	170 / 110	140 / 90		
4	55	W	1 mo.	No	170 / 110	170 / 110	155 / 90	2 months	160 / 100
5	67	N	7 mo.	Yes	190 / 110	170 / 90	135 / 85		
6	58	N	3 mo.	Yes	200–195 / 115–105	195 / 105	140 / 90	7 months	180 / 100
7	60	N	1 mo.	No	170 / 100	170 / 100	160 / 105	3 months	160 / 100
8	56	N	1.5 yr.	Yes	200–210 / 130	210 / 130	200 / 135	1 month	210 / 135
9	62	N	1 yr.	Yes	160–165 / 90–100	165 / 100	160 / 90	4 months	160 / 80
10	46	N	1 mo.	No	170 / 105	170 / 105	140 / 90		
11	52	W	1.5 yr.	Yes	160–180 / 90–110	170 / 100	138 / 88	4 months	145 / 90
12	46	W	2 yr.	Yes	140–160 / 90–115	160 / 115	140 / 90	3 months	140 / 100
13	26	W	6 mo.	Yes	160–180 / 100–110	170 / 100	150 / 90	4 months	160 / 90
14	80	W	6 mo.	No	170–180 / 90–100	180 / 100	140 / 80	3 months	140 / 80
15	60	W	1 mo.	No	170–180 / 90–110	170 / 90	150 / 80	6 months	170 / 100
16	46	W	1 mo.	Yes	200–230 / 120–130	200 / 130	170 / 120	1 month	170 / 120
17	43	W	1 mo.	No	160–170 / 110–120	160 / 110	170 / 120	2 months	170 / 120
18	70	W	3 mo.	Yes	170–180 / 100–110	170 / 110	150 / 90	2 months	170 / 100
19	56	W	2 yr.	Yes	200–240 / 100–140	230 / 130	230 / 130		
20	60	W	1 mo.	Yes	190–210 / 120–130	190 / 130	190 / 120	2 months	200 / 130
21	70	W	1 mo.	No	170 / 100	170 / 100	150 / 90		
22	70	W	2 wk.	No	170 / 100	170 / 100	155 / 95		

TABLE 1—*Continued*

Case No.	Age, yr.	Race	Treatment and Observation Before Sex Hormone Therapy			Effect of Sex Hormone Therapy on Blood Pressure		Subsequent Observation	
			Time	Treatment	Blood pressure range, mm. Hg	Beginning of treatment, mm. Hg	End of treatment, mm. Hg	Time after sex hormone therapy discontinued	Blood pressure, mg. Hg
23	42	W	5 mo.	Yes	210–180 120–110	180 110	180 110	3 months	200 115
24	53	W	2 mo.	Yes	200–180 120–115	180 115	150 100	6 months	170 110
25	68	N	3 mo.	Yes	260–240 140–130	240 130	200 110		
26	38	N	1 wk.	No	200–190 110–105	190 105	160 90		
27	47	W	2 wk.	No	180–170 110	170 110	138 90	3 months	150 100
28	51	W	6 mo.	Yes	220–210 150–140	210 140	190 120	3 months	200 130
29	43	W	1 wk.	No	200 110	200 110	160 90		
30	51	N	2 mo.	Yes	170–150 110–95	160 105	135 85		

analysis were negative; specific gravity was 1.022. Roentgenogram of the heart and great vessels revealed slight widening and tortuosity of the aorta and early left ventricular enlargement. Findings on concentration and dilution tests of renal function were normal. The peripheral arteries showed diffuse thickening, grade I. The blood pressure was 200 mm. Hg, systolic and 115 diastolic. Treatment for the next 3 months consisted of a), partial rest; *b*) maintenance diet, relatively low in fat content; *c*), aminophyllin 3 grains, 3 times a day; and *d*), small, regular doses of phenobarbital. At the end of this time he felt somewhat better but still had occasional headaches and dizziness. The blood pressure was 195 mm. Hg. systolic and 105, diastolic. All other treatment was suspended and testosterone propionate by intramuscular injection was begun. A placebo was substituted for the phenobarbital. Blood pressure readings progressively decreased and in the 8th week the blood pressure was 140 mm. Hg systolic and 90 diastolic. He volunteered the information that he felt stronger and generally better than he had in 10 years. Attacks of headache and dizziness stopped after the 3rd week of androgenic therapy. Seven months after the cessation of treatment he returned to the clinic complaining of a recurrence of headaches; the blood pressure was 180 mm. Hg systolic and 100 diastolic.

N. S., a male, white, age 42, complained of attacks of pounding in the chest, irritability and roaring in the head. Past medical history was insignificant except for one attack of pyelitis. The blood pressure was 210 mm. Hg systolic and 120, diastolic; the pulse was rapid with a rate of 100. Peripheral arteries and eye grounds were normal. The urine was normal with a specific gravity of 1.019; renal function was normal as measured by concentration and dilution tests. Retrograde pyelograms revealed no evidence of renal or ureteral disease. The electrocardiographic curves were within normal limits and a roentgenogram of the thorax was considered to be normal. The basal metabolic rate was −2 per cent.

Theocalein, 15 grains, 3 times a day, along with small doses of phenobarbital, was prescribed and 10 weeks later the nervous symptoms had improved, although he still complained of palpitation, fullness, and roaring in the head. The blood pressure was 190 mm. Hg. systolic and 110, diastolic. The theocalein was replaced by potassium thyocyanate administered in sufficient dosage to maintain a blood level between 8 and 12 mg. per cent. Eight weeks later he complained of dizziness, nausea, weakness, and considerable subjective nervousness. The blood pressure was 180 mm. Hg systolic and 110, diastolic; the blood thiocyanate was 11 mg. per cent. All other therapy was discontinued and treatment with male hormone begun. At the end of another 10 weeks he was extremely pleased with his condition, stating that the disagreeable sensations in his head and chest had ceased to occur, and that all subjective nervousness had disappeared. The blood pressure was 180 mm. Hg systolic and 110, diastolic.

Effect on Cerebral Circulation

Evidence in the form of subjective improvement has accumulated in the process of this study suggesting that sex hormones may improve cerebral circulation in some hypertensive individuals. Sixteen patients complained of minor symptoms of probable cerebral origin such as headaches, severe headache

TABLE 2. EFFECT OF ESTROGENIC SUBSTANCE ON BLOOD PRESSURE IN FEMALE PATIENTS WITH ESSENTIAL HYPERTENSION

Case No.	Age, yr.	Race	Treatment and Observation Before Sex Hormone Therapy			Effect of Sex Hormone Therapy on Blood Pressure		Subsequent Observation	
			Time	Treatment	Blood pressure range, mm. Hg	Beginning of treatment, mm. Hg	End of treatment, mm. Hg	Time after sex hormone therapy discontinued	Blood pressure, mm. Hg
Estradiol dipropionate									
1	44	W	2 yr.	Yes	230–270 / 120–140	230 / 130	240 / 130	Still being treated	
2	62	N	1 mo.	No	170–180 / 95–110	165 / 100	135 / 85	6 months	145 / 90
3	63	W	6 mo.	Yes	160–170 / 90–100	170 / 100	140 / 90	3 months	150 / 90
4	58	W	1 yr.	Yes	170–180 / 90–100	170 / 90	150 / 80	3 months	150 / 80
5	50	W	2 mo.	Yes	160 / 90	160 / 90	135 / 84	4 months	140 / 90
6	46	W	1 wk.	No	220 / 140	210 / 130	190 / 110		
7	47	W	2 mo.	Yes	160–170 / 100–110	160 / 100	130 / 80	2 months	130 / 80
8	55	W	2 mo.	Yes	180–190 / 110–100	180 / 100	145 / 85	2 months	150 / 90
9	37	N	6 mo.	Yes	170–260 / 110–140	180 / 115	180 / 115	Still being treated	
10	46	N	1 mo.	No	170 / 110	170 / 110	148 / 100		
11	50	N	1 wk.	No	300 / 170	300 / 170	260 / 155	Still being treated	
12	60	W	2 yr.	Yes	200–210 / 100–110	205 / 110	165 / 85	Still being treated	
Mixed estrogens									
13	55	N	1 yr.	Yes	150–160 / 90–100	150 / 90	110 / 70	8 months	160 / 90
14	60	N	1.5 yr.	Yes	160–210 / 100–130	160 / 110	145 / 110		
15	50	N	1 mo.	No	190 / 115	190 / 115	145 / 100	2 months	160 / 100
16	30	N	6 mo.	Yes	140–150 / 90–110	150 / 110	120 / 80	2 months	135 / 100
17	48	N	6 mo.	Yes	160–190 / 90–100	180 / 100	170 / 100		
18	42	N	3 yr.	Yes	200–230 / 100–140	210 / 140	210 / 140	Still being treated	
19	41	N	2 yr.	Yes	170–190 / 115–120	170 / 115	150 / 100		
20	62	W	6 mo.	Yes	210–250 / 110–140	210 / 120	165 / 90	1 month	180 / 100

TABLE 2—*Continued*

Case No.	Age, yr.	Race	Treatment and Observation Before Sex Hormone Therapy			Effect of Sex Hormone Therapy on Blood Pressure		Subsequent Observation	
			Time	Treatment	Blood pressure range, mm. Hg	Beginning of treatment mm. Hg	End of treatment mm. Hg	Time after sex hormone therapy discontinued	Blood pressure, mm. Hg
21	52	W	6 mo.	Yes	165–180 / 95–100	170 / 90	150 / 85	1 month	150 / 85
22		N	1 yr.	Yes	220–230 / 110–140	210 / 120	210 / 120	2 months	210 / 120
					Estrone				
23	46	W	1 yr.	Yes	180–150 / 100–90	170 / 90	150 / 90	2 months	150 / 90
24	60	W	1 wk.	No	210–200 / 110	200 / 100	145 / 90	3 months	180 / 100
25	51	W	3 mo.	Yes	160–170 / 110	160 / 110	160 / 100	4 months	160 / 100
26	64	W	1 wk.	No	180 / 120	180 / 120	155 / 100		

associated with nausea, dizziness, blurring of vision, irritability, subjective nervousness, insomnia, and sensations of fullness and heaviness in the head. Twelve patients in this group obtained symptomatic relief, while 4 were not improved. Six individuals exhibited the more severe cerebral phenomena associated with transient episodes of marked blood pressure elevation (hypertensive encephalopathy); the severity and frequency of such attacks were definitely reduced in 4 individuals while the other 2 were not benefited.

The effect of the sex hormones on the attitude, disposition and mental capacity in some individuals suggests improved cerebral circulation. The return of selfconfidence and courage, increase in mental acuity and mental capacity, return of emotional stability and the evolution of a general sensation of well being have been common observations in this series of patients. Such a response is not unusual in the manifestly hypogonadal individual as a result of replacement therapy. Hence, these results cannot be properly accredited to improvement in cerebral circulation. Improvement of cerebral circulation, however, may be the mechanism by which this result is achieved with replacement therapy in hypogonadism.

Patients presenting evidence of definite brain tissue necrosis usually showed no improvement other than that which might have been expected to occur under any other reasonable method of treatment. Four male patients have had cerebral-vascular accidents while being treated with male hormone. One died immediately; the other 3 lived and treatment with male hormone was continued. Progress in these 3 did not appear to be influenced in any way by male hormone therapy.

CASE REPORTS

C. B., a female negro, age 37, complained of recurrent attacks of severe headache accompanied by nausea and vertigo, and followed by spells of unconsciousness. The blood pressure was 210 mm. Hg. systolic and 130, diastolic; the peripheral arteries showed thickening and sclerosis, grade II. Retinal arterioles showed evidence of high grade sclerosis and one area in the left eye ground had been the site of a previous hemorrhage. Roentgenograms of the skull showed no abnormality. The spinal fluid was normal except for a slight increase in pressure. The urine showed a trace of albumen and had a specific gravity of 1.028. Intravenous pyelograms revealed nothing abnormal. Other laboratory findings were within normal limits. During the next 6 weeks, while the patient was taking a xanthine preparation along with phenobarbital and potassium iodide, she had 6 severe attacks such as described above. One of these occurred while she was in the clinic and the blood pressure during the episode was 280 mm. Hg systolic, 140 diastolic. The xanthine drug was discontinued and estradiol dipropionate was substituted. In the following month she had two more attacks; in the succeeding two months she experienced only one and it was milder than previous attacks. Two months later she stated that other than an occasional severe headache she had been quite well. The blood pressure was 170 mm. Hg systolic and 115, diastolic.

J. S. W., a white male age 57, complained of loss of strength, extreme subjective nervousness, intense headache and shortness of breath on unusual exertion. He also complained that he was unable to carry on his job as a

shipping clerk because of inability to concentrate on his work. Significant findings on complete examination were as follows: Blood pressure 170 mm. Hg, systolic and 110, diastolic; peripheral, aortic, and retinal arteriosclerosis, grade II. Renal function was normal. Blood Wassermann and spinal fluid Wassermann reactions were negative. Testosterone propionate was administered by intramuscular injection for 8 weeks. At the end of this time he could think clearly and carry on his work with efficiency; headaches still occurred but were much less severe; the blood pressure was 150 mm. Hg systolic and 90, diastolic. Male hormone therapy was discontinued and he was advised to take, regularly, potassium iodide, aminophyllin, and small doses of phenobarbital. Four months later he began to experience severe headaches again, became extremely nervous and could not concentrate on his work long enough to add up a small column of figures. Two days later he had a cerebral-vascular accident result in paralysis of the right arm and leg. In the course of 3 months recovery from this incident seemed fairly complete although he still complained of headaches, nervousness and difficulty in mental concentration. Male hormone therapy was begun again and two months later the patient felt much improved, being able to do his work satisfactorily. The blood pressure was 155 mm. Hg systolic and 88, diastolic.

Effects on Coronary Circulation

Twelve patients exhibited characteristic angina pectoris. Of 3 women in this group, 2 were improved on sex hormone therapy, while one individual continued to have frequent attacks of chest pain. Shortly after cessation of treatment this patient died from a coronary thrombosis. Among 9 male patients 7 were definitely improved by testosterone propionate therapy, while 2 individuals were not benefited. One of these who did not improve had a myocardial infarction during treatment with the sex hormones. Improvement, when it occurred, was manifested by an increase in tolerance to all precipitating factors, an increase in strength, and in some cases considerable decrease in the severity of pain when attacks occurred. The response to sex hormone therapy among patients with angina pectoris in this series was not so uniformly favorable as Lesser (4), Bonnell et al. (3), and Hamm (5) obtained.

Five male patients exhibiting attacks of paroxysmal nocturnal dyspnea have been treated with testosterone propionate. One of these individuals had a relatively low blood pressure (100/70). During sex hormone therapy he obtained complete relief from the attacks of cardiac asthma, along with a moderate elevation of the blood pressure (160/90). Of 4 hypertensive individuals 2 obtained definite improvement while 2 were not benefited.

Fifteen patients complained of loss of strength, undue fatigue, and shortness of breath on unusual exertion. A general increase in strength and a specific increase in exercise tolerance occurred in 11 of these individuals following sex hormone therapy. While dyspnea on unusual exertion is a cardinal feature of early heart failure, actual proof that relief of this symptoms was related to improved myocardial function is obviously lacking. Improved myocardial nutrition incident to an augmentation of coronary flow, however, may have been the effective mechanism.

CASE REPORTS

O. E. F., age, 52, a white male exhibited a typical clinical picture of angina pectoris, chest pain being routinely precipitated upon walking 3 blocks. He also complained of recent loss of strength, undue fatigue and insomnia. The blood pressure was 170 mm. Hg systolic and 110 diastolic; the peripheral arteries showed slight thickening; tonsils were enlarged and chronically infected. Electrocardiogram, teleoroentgenogram and other essential laboratory studies yielded normal findings. This man was studied for 18 months in the clinic during which time the tonsils were removed and he received, continuously, potassium iodide, theobromine, and phenobarbital. At the end of this period he complained that attacks of angina were more severe and more frequent. The blood pressure was 165 mm. Hg systolic and 100, diastolic. Potassium iodide and theobromine were discontinued. In the following 3 months he regularly received injections of testosterone propionate. The resulting subjective improvement was marked. He obtained sufficient relief from the attacks of pain to accept a job at light labor and was able to carry on this work without discomfort. At the end of the period of treatment with the androgenic substance, the blood pressure was 125 mm. Hg systolic, and 85, diastolic. He continued to work and 5 months later reported rare attacks of chest pain which he thought could be precipitated by walking a distance of 8 blocks. The blood pressure was 130 mm. Hg systolic and 90, diastolic.

L. L. K., age 58, male white whose complaint was deep aching chest pain radiating to left shoulder; this discomfort was always precipitated by unusual exertion; it was frequently induced by emotional upset, and rarely came on while at rest. He further complained of intermittent claudication in the calf and thigh muscles of both legs precipitated by walking one-half block. The past medical history revealed that 5 years before he had suffered a severe attack of chest pain followed by faintness, cyanosis and marked sweating. This attack was diagnosed as myocardial infarction; he gradually improved and felt normal again 6 months later.

Essential findings on physical and laboratory survey were generalized arteriosclerosis, marked impairment of the circulation of both lower extremities, with cyanotic cold feet. The posterior tibial pulsation could not be elicited in either foot, while the dorsalis pedis pulsations were barely perceptible. The blood pressure was 120 mm. Hg systolic and 80, diastolic. The electrocardiographic curves were normal. Testosterone propionate therapy was instituted along with mild sedation. After one month of treatment the patient complained that attacks of chest pain were more severe and more frequent. Treatment was continued and 2 weeks later he was seized with a brief

severe, headache and dizziness followed shortly afterward by paralysis of the left arm. He was hospitalized and treatment with male hormone continued. Three weeks later he had regained the use of the left arm but complained of substernal pain on the slightest exertion. A few days later he was seized with a severe chest pain which lasted 18 hours; a subsequent electrocardiographic tracing clearly indicated a recent infarction of the anterior heart wall.

Mrs. P. E. L., age 63, a white female, complained of a crushing, substernal pain radiating to the base of the neck and down the left arm. This discomfort was always precipitated by walking up one flight of stairs, by anger or excitement, and frequently occurred after a heavy meal. Physical examination and the laboratory survey substantiated the diagnoses of hypertensive and arteriosclerotic cardiovascular disease with angina pectoris. The blood pressure was 170 mm. Hg systolic and 100, diastolic. During the next 3 months the patient followed a medical program including *a*), partial bed rest, *b*), maintenance diet, low in cholesterol and fat, *c*), aminophyllin 3 grains, 3 times a day, 0.5 grains of phenobarbital 3 times a day, and *d*), nitroglycerin for relief of attacks. At the end of this time she felt somewhat improved, anginal attacks occurring only when she walked 4 blocks or climbed 2 flights of stairs. The blood pressure was 160 mm. Hg systolic and 95, diastolic. In the following 3 months the only medication the patient received was estrogenic substance, placebos being substituted for the aminophyllin and phenobarbital. During and at the end of this program of treatment she obtained complete relief from the anginal attacks and was able to walk two miles without untoward effect. The blood pressure at the last visit was 140 mm. Hg systolic and 90, diastolic.

Effect of Peripheral Circulation

Fourteen patients with organic peripheral vascular disease were treated with androgenic and estrogenic substances. In this group 8 individuals showed marked improvement, 2 responded fairly well, and 4 were not benefited. In 2 patients, with characteristic thrombo-angiitis obliterans, the results were unusually good. In the arteriosclerotic group, 2 female and 4 male patients showed definite improvement, while 2 men were relieved of pain but still presented objective evidence of impaired circulation. Three men and one woman in the arteriosclerotic group were not obviously helped by the treatment with androgenic or estrogenic substance. In all 4 of these who showed no improvement vascular involvement was extensive.

CASE REPORTS

J. N. L., age 40, white male. This patient complained of severe claudication in the left calf after walking 4 blocks, and painful ulcers on the left great and fourth toes. Claudication had begun 3 years before and the ulceration was of 2 months' duration. Both feet and lower legs were cold and cyanotic. Cyanotic rubor appeared on dependency and unusual blanching on elevation. Gangrenous ulceration involved the tip of the great toe and the distal one-half of the fourth toe. No pulsations were demonstrable in the pedal arteries of the left foot, the left popliteal, and the right posterior tibial. Ossilometric indices were: Left ankle, ½; just below left knee, 2; left mid-thigh, 3; right ankle, 1; just below right knee, 3; right mid-thigh, 5. Active phlebitis was present in the right leg. Treatment consisted of male hormone only. At the end of 4 months the ulcer on the great toe had healed, the fourth toe had sloughed off and the stump had healed. The patient could walk 5 miles without pain. The color and apparent temperature (by palpation) of the feet and legs was much improved, although moderate cyanosis was still demonstrable on dependency, and unusual blanching on elevation. The ossilometric indices were: Ankle, 2½; just below left knee, 4; left mid-thigh, 4; right ankle, 3; just below right knee, 4; right mid-thigh, 5.

L. T., age 73, a white male, complained of continuous excruciating pain and ulceration of the right foot. He had experienced pain in the calf of the leg on walking for the previous 2 years, and had been unable to keep his feet warm in cold weather for the past 5 years. The entire right leg was cold and slightly cyanotic. There was an area of deep ulceration involving the plantar and lateral aspects of the right foot at the base of the small toe. Pulsations were not palpable in the pedal, popliteal, or femoral arteries of the right lower extremity. Ossilometric indices were: right ankle, 0; just below right knee, 0; mid-thigh ½. Male hormone was administered by intramuscular injection. This therapy was continued for 2 months without any evidence of improvement. There was no relief from the pain and the gangrenous ulcer was larger at the end of treatment than it had been in the beginning.

DISCUSSION

In an attempt to evaluate a given chemotherapeutic substance in the treatment of primary hypertension one is faced with the difficult task of distinguishing between the psychotherapeutic and the pharmacodynamic properties of the remedy in question. The physiological background for so-called essential hypertension probably is an inherent neurogenic defect which, prior to the establishment of irreversible vascular changes, is manifested by unusual vasomotor irritability (9, 10). While it is well known that these individuals exhibit an exaggerated vasoconstrictor response to disagreeable psychic stimuli, it is often overlooked that agreeable psychic stimulation can provoke the opposite vasomotor reaction with a consequent fall in blood pressure. This highly susceptible neurovascular mechanism accounts for the fact that some lowering of the blood pressure along with subjective improvement can be effected in patients with essential hypertension by almost any therapeutic procedure which includes, among its more pertinent features, a liberal measure of reassurance.

While psychotherapy unquestionably has played an important rôle in this study, certain findings indicate that the sex hormones exert a definite and a sustained vasodilating action. The majority of the

patients in this investigation were being treated by other methods when sex hormone therapy was initiated, and in many of these a further lowering of the blood pressure occurred. In the entire group of hypertensive individuals, sex hormone therapy has resulted in a more pronounced and more prolonged lowering of the blood pressure than I have usually obtained by other medical methods. Moreover, the effect of these substances in occulsive peripheral vascular disease and angina pectoris is further indicative of a pronounced vasodilating action.

Subjective improvement among these patients has been more evident than is usually observed as a result of other therapeutic methods. Such phenomena are difficult to evaluate since they are not amenable to any known accurate method of study. Nevertheless, relief of distressing symptoms is a highly desirable result and, alone, may be conducive to further vascular relaxation. Hamm has discussed this point briefly and excellently (5).

The data presented in this study favor the concept of a direct vasodilating action of the sex hormones. This is a reasonable explanation of the relief of vasospastic cerebral phenomena, improvement in the anginal syndrome, the favorable effect on the peripheral vascular system, and the fall in blood pressure in some hypertensive patients. A direct vasodilating action is not, however, in keeping with the fact that the blood pressure is occasionally elevated in hypotensive individuals as a result of sex hormone therapy; nor will it explain the usual failure of these substances to affect the normal blood pressure (2, 11, 12). In a consideration of the menopausal syndrome it is difficult to explain the variety of vascular disturbances which occur in this manifestly hypogonadal state entirely on the basis of deficiency of a hormone whose essential vascular action is vasodilation (13–16). It is consistent with the known facts concerning vasomotor instability in the climacteric to reason that gonadal dysfunction may produce an endocrine imbalance which, shifted in one direction provokes vasoconstriction and, shifted in another, causes vasodilation. While the gross mechanism by which the sex hormones favorably influence vasospastic phenomena is obviously vasodilation, the finer mechanism may be the establishment of an endocrine balance.

The findings in this survey strongly suggest that the sex hormones are useful chemotherapeutic remedies for the management of patients with essential hypertension, angina pectoris, and peripheral vascular disease. The utility of the androgenic and estrogenic substances in cardiovascular disease appears to be directly related to the property of these substances for effecting vasodilation.

SUMMARY

1. The pertinent literature on the use of the sex hormones in cardiovascular disease is briefly reviewed.

2. Results in the treatment of 82 individuals with androgenic and estrogenic substances are reported; these patients exhibited the following clinical syndromes: 56 patients had essential hypertension; 12 had angina pectoris; and 14 had organic peripheral vascular disease.

3. The results are briefly discussed, attention being directed to the probable psychotherapeutic as well as pharmacodynamic properties of the sex hormones.

4. The sex hormones appear to be valuable chemotherapeutic substances in essential hypertension, angina pectoris, and organic peripheral vascular disease.

498 Orleans Street,
Beaumont, Texas.

REFERENCES

1. Edwards, E. A., J. B. Hamilton and S. Q. Duntley: Testosterone propionate as a therapeutic agent in patients with organic disease of the peripheral vessels. Preliminary report. *New England J. Med.* 220: 865. 1939.
2. Walker, T. C.: The use of testosterone propionate and estrogenic substance in cardiovascular disease: preliminary report. *Med. Rec. & Ann.* 34: 667. 1940.
3. Bonnell, R. W., C. P. Pritchett and T. E. Rarden: Treatment of angina pectoris and coronary artery disease with sex hormones. *Ohio State M. J.* 37: 554. 1941.
4. Lesser, M. A.: The treatment of angina pectoris with testosterone propionate: preliminary report. *New England J. Med.* 226: 51. 1942.
5. Hamm, L.: Testosterone propionate in the treatment of angina pectoris. *J. Clinical Endocrinology* 2: 325. 1942.
6. Steinach, E., O. Peczenik and H. Kun: Über hormonale Hyperamisierung, insbesondere uber den Einfluss der männlichen sexual Hormone und ihrer Kombination mit weiblichem Hormon auf erhohten Blutdruck und Hypertonus. *Wien. klin. Wchnschr.* 51: 65; 102, 134. 1938.
7. Arndt, H., Zur Therapie extragenitaler Storungen mit Sexualhormonen. *Wien. med. Wchnschr.* 89: 222. 1939.
8. Greene, R.: On the effect of testosterone propionate on blood pressure. *Lancet* 2: 79. 1938.
9. Miller, J. H., and M. Bruger: The Cold-pressor reaction in normal subjects and in patients with primary (essential) and secondary (renal) hypertension. *Am. Heart J.* 18: 329. 1939.
10. Robinson, S. C., and M. Brucer: Range of normal blood pressure. A statistical study of 11,383 persons. *Arch. Int. Med.*: 64: 409. 1939.
11. Deck, M., and C. W. Hooker: The absence of acute effects of the sex hormones. *J. Lab. & Clin. Med.* 25: 33. 1930.
12. Partington, P. F., and I. T. Nathanson: Action of estrin on the blood pressure of the anaesthetized cat. *Endocrinology* 25: 71. 1939.
13. Scherf, D.: The respiration and the circulatory system in females with ovarian dysfunction. *Ann. Int. Med.* 12: 1414. 1940.
14. Turner, H. H.: The clinical use of synthetic male sex hormone. *Endocrinology* 24: 763. 1939.
15. Werner, A. A.: The male climacteric. *J. Am. Med. Assoc.* 112: 1441. 1939.
16. Schaefer, R. L.: Menopausal hypertension. *Endocrinology* 19: 705. 1935.

Sublingual Administration of Diethylstilbestrol; Comparison of Routes in Therapy

[Estrogens and Menopause]

DANTE CASTRODALE, M.D., ELLEN LOEFFEL, M.D. AND CYRIL M. MACBRYDE, M.D.

From the Department of Medicine, Washington University School of Medicine, the Washington University Clinics and the Barnes Hospital, Saint Louis, Missouri

DESPITE THE FACT that diethylstilbestrol is highly effective as an estrogen when taken orally, in certain instances other routes of administration may be preferable. Intramuscular injection may be the treatment of choice in some cases when termination of lactation is desired, when large doses must be given and the duration of treatment is short. Injection will seldom be the method of choice for maintenance therapy because of the inconvenience, pain and greater expense as compared to the oral route. Subcutaneous implantation of pellets is practical and effective, as we have previously reported (1), but is preferred by only a small percentage of patients. It is desirable also to be able to interrupt estrogen therapy easily and at will. There is much evidence to suggest that regularly interrupted or cyclic administration of estrogen may prove to be the most logical mode of therapy, and to give the best clinical results (2).

Certain hormones are absorbed quickly into the sublingual venous plexuses. In the instances of desoxycorticosterone (3) and estradiol (4, 5) the demonstration that the sublingual route is effective is of considerable importance, because of the very poor absorption of these substances from the gastrointestinal tract and their consequent oral inefficacy. Although this indication for trying sublingual therapy with diethylstilbestrol does not exist, we decided to study the response of patients to treatment by this route, *a*), to determine the relative effectiveness of the sublingual as compared with the oral and intramuscular routes; *b*), to provide an alternative method for patients who dislike swallowing tablets; *c*), to determine whether the incidence of nausea as compared with that following oral therapy might be diminished.

Received for publication July 29, 1942.

METHODS

Seventeen women suffering from typical symptoms of estrogen deficiency were chosen for this study. The chief complaints were similar in all of these cases and were chiefly hot flushes, headaches, nervousness, fatigue, insomnia and emotional instability. The cause of the hypo-estrinism was spontaneous menopause in 12 of the 17, removal of the ovaries in 4, and radium therapy to the pelvic organs in 1. Two of the patients were over 50 years of age, 8 were between 40 and 50, 6 between 35 and 40, and 1 under 35.

Diethylstilbestrol in propylene glycol[1] (20 mg. to the cc.) was administered by dropping the solution under the tongue with a medicine dropper. The droppers used delivered 40 drops to the cc., so that 1 drop twice daily, for example, gave a daily dose of 1.0 mg. Patients were cautioned not to swallow the material, being instructed to spit out any excess fluid present in the mouth after allowing 4 minutes for absorption. The dose used in most cases was 2 drops daily for 2 weeks, followed by a 2-week interval without medication, with regular repetition of the cycle. In a few patients 4 drops (2.0 mg.) daily were given for the 2-week period. A few patients required longer periods of treatment, and shorter intervals without medication to insure good relief of symptoms. Results were judged by *a*), the relief of symptoms, and *b*), the changes in the vaginal smears. No patient is included in this analysis who was not treated with the drops for at least 1 month. Five were treated for 3 months, 4 for 6 months, 1 for 9 months, 1 for 14 months.

RESULTS

Good relief of symptoms was obtained in 11 of the 17 cases. In judging the degree of relief, comparison

[1] Diethystilbestrol in propylene glycol was supplied by the Department of Medical Research of the Winthrop Chemical Co., 170 Varick St., New York City.

was made with the improvement following oral diethylstilbestrol therapy or parenteral administration of the natural estrogens to the patient during other periods of study. The degree of symptomatic relief was poor in 6 cases. In 4 of these 6 cases nausea was so troublesome that treatment was discontinued. Eight of the 17 patients experienced nausea at some time during the course of sublingual therapy. In 3 instances this was temporary and good results without nausea were obtained with continued treatment. We have never encountered such a high incidence of nausea with orally administered diethylstilbestrol, our figures being 20 per cent for continuous medication, but only 8.6 per cent with the interrupted method (2). Nausea was sufficient to make sublingual therapy impractical in 5 of the 17 cases, or 30 per cent, even when the mode of interrupted treatment was used. It seems likely that the unpleasant taste of the material may have increased the frequency of this symptom.

Vaginal smear response was definite in all cases, the estrogenic effects of the material administered sublingually differing little from that obtained by the same doses given orally. Sublingual therapy proved to be no more effective per milligram administered than when given by the oral route, as judged by the effects on the vaginal smears. One mg. per day by mouth is approximately equivalent to 1.0 mg. per day when given sublingually or 0.5 mg. intramuscularly, as judged by 'human assay' as performed on this and previous groups of our patients.

Of the 11 patients obtaining good results, 1 required continuous therapy with 1.0 mg. sublingually. She has taken this steadily for over 14 months. This patient had had an artificial menopause produced by radium 3 years before onset of treatment. Her menopausal symptoms had been so severe that she was unable to obtain and hold a job even though it was economically necessary for her to do this. Hot flashes would occur 3 to 4 times nightly, and would be strong enough to waken the patient and disrupt sleep. Nervousness was acute; she was unable to talk without a quaver in her voice, was unable to mix and talk with people without crying. Partial relief had been obtained with the use of diethylstilbestrol in tablets, but the severe nausea encountered made it necessary for the patient to interrupt treatment so often that the vaginal smear rarely changed to more than 1+. However, she was able to take the drops continuously without nausea. The vaginal smear changed from 0 to 4+ and has remained so until the present time. She has now secured and holds a fairly good position and has become socially adjusted again.

Two patients required 4 drops (2.0 mg.) daily for 2 weeks, when alternated with a 2-week period without treatment, while 6 patients did well with 2 drops (1.0 mg.) on this schedule. Two patients did best when the drops were given for 3 weeks, and omitted for only 1 week. No other untoward symptom and no evidence of toxicity except nausea was observed in any of the 17 patients.

SUMMARY

1. Diethylstilbestrol in propylene glycol administered sublingually gave a positive vaginal smear response in all of 17 cases of hypo-estrinism.

2. Relief of symptoms was good in 11 cases; poor in 6.

3. The chief cause of failure of symptomatic improvement was nausea. Nausea occurred much more frequently with sublingual than with oral therapy.

4. Per milligram of the diethylstilbestrol administered, sublingual therapy is approximately equivalent to oral therapy while intramuscular injection is approximately twice as effective.

5. In a small percentage of patients sublingual diethylstilbestrol therapy may prove preferable to the oral or intramuscular routes, or to pellet implantation. Oral administration remains the treatment of choice in the great majority of patients.

REFERENCES

1. MacBryde, C. M., H. Freedman, E. Loeffel and D. Allen: Estrogenic therapy by implantation of stilbestrol pellets, *Proc. Soc. Exper. Biol. & Med.* 43: 212. 1940.
2. MacBryde, C. M., D. Castrodale, E. Loeffel and H. Freedman: The synthetic estrogen diethylstilbestrol; clinical and experimental studies (II). *J. Am. Med. Assoc.* 117: 1240. 1941.
3. Anderson, E., W. Haymaker and E. Henderson: *J. Am. Med. Assoc.* 115: 2167. 1940.
4. Salmon, V. J., and S. H. Geist: *Proc. Soc. Exper. Biol. & Med.* 45: 766. 1940.
5. Hall, G. J.: *J. Clinical Endocrinology* 2: 26. 1942.

A Spermatozoal Stain for Clinical Studies[1]

W. Kenneth Cuyler, Ph.D.
and Margaret Baptist

From the Endocrine Division of the Department of Obstetrics and Gynecology, Duke University School of Medicine and Duke Hospital, North Carolina

Numerous methods have been described for staining human spermatozoa. Some of these produce excellent results. As a rule, however, the methods which give the best results require several hours or days for completion. This fact makes them more suited to research problems than to clinical studies.

Technicians not uncommonly experience difficulty in reproducing results when employing the staining methods of other workers. In our laboratory we have not been able to produce satisfactory stains with any one of several generally accepted clinical methods for staining smears of human seminal fluid. We have developed, therefore, a method for clinical use which has proved satisfactory in our hands. This report presents the details of this method.

Method

Smears of the seminal fluid are made, as soon as the specimen has liquefied, by drawing a drop of seminal fluid over a glass slide with the end of another slide. The smears are fixed by passing the slides several times through a flame. Staining may be done at this point, or the smears may be stored for future study.

Three stains are utilized,[2] two of which are to be found commonly in the clinical laboratory. These two are hematoxylin and eosin. The third stain, fast green, is readily available although it is not in general use.

Procedure

After the smear is fixed with heat, the staining technic proceeds throughout in Coplin jars as follows.

1). Let stand in 95% alcohol[3] 5 to 10 minutes.
2). Wash out excess alcohol in tap water.
3). Stain for 1 minute in Harris' hematoxylin (Harris' hematoxylin, 1 part; 8% alcohol, 3 parts). In making up the original stock solution of Harris' hematoxylin, 4 cc. of glacial acetic acid are added to 100 cc. of stain.
4). Rinse out excess hematoxylin in distilled water.
5). Destain 5 to 7 seconds in acid alcohol (concentrated hydrochloric acid, 1 cc.; 95 cc. of 70% alcohol).
6). Rinse thoroughly in distilled water.
7). Transfer to weak alkaline water (ammonium hydroxide, specific gravity 0.90, 2 drops; tap water, 60 cc.) for 5 to 10 seconds.
8). Rinse in distilled water.
9). Counter-stain in eosin (eosin 'Y,' 1 gm.; 25% alcohol, 95 cc.) for 3 minutes.
10). Rinse quickly in distilled water.
11). Counter-stain in a 1% aqueous solution of fast green for 15 to 20 seconds.
12). Rinse in 95% alcohol; leave stain streaking on slide.
13). Rinse in absolute alcohol until, upon gross inspection, the green dye has been washed out. This is a matter of a few seconds.
14). Clear for 3 minutes in xylol.
15). Mount in balsam.

The spermatozoa are differentiated by this stain as follows: acrosome, lavender; nucleus, pink; body and tail, green. The technique requires less than 25 minutes to execute.

Discussion

There are but few critical steps in this staining procedure. The fast green has a tendency to wash out the eosin. It is advisable, therefore, not to rinse the smear too thoroughly between the eosin and the green dye, nor to leave the smear longer than the stipulated time in the solution of fast green. Occasionally, smears made of seminal specimens which are particularly mucoid are difficult to stain satisfactorily. Such a smear can be stained with some success if first Williams' (1) method of mucus liquefaction is applied.

A high percentage of seminal fluids contain spermatozoa which are morphologically normal in appearance, but which are not stained by this method. Multiple smears made from the same seminal specimen show approximately the same percentage of these spermatozoa. The percentage varies greatly between seminal specimens. The significance of this finding is being studied.

We have found that smears which have been stored for several weeks stain as well as freshly made ones,

Received for publication June 28, 1942.
[1] Part of the expenses of this study was defrayed by a grant to one of us (M. B.) from the Research Council of Duke University.
[2] The hematoxylin, eosin-Y and fast green (certified) were obtained from the National Aniline and Chemical Co., Inc., New York City.
[3] No methanol is used in this method.

and that smears made from seminal fluid which has been refrigerated several days also stain well.

This method of staining smears of seminal fluid has several features which are of some importance to the clinician. *a*). The procedure may be completed in 25 minutes or less. *b*). Results can be duplicated by technicians unfamiliar with the procedure. *c*). Spermatozoa are stained differentially with regard to their morphologic characteristics. *d*). Freshly prepared smears or old ones stain equally well. *e*). Readily obtainable stains are employed.

SUMMARY

A staining method is described for use in clinical studies of human seminal fluid. Harris' hematoxylin and the counterstains, eosin-Y and fast green are employed. The spermatozoa are differentiated morphologically. The technic requires less than 25 minutes to complete.

REFERENCES

1. WILLIAMS, W. W.: *New England J. Med.* 217: 946. 1937.

COMMUNICATIONS TO THE EDITORS

Treatment of Amenorrhea with Diethyl-Stilbestrol and Chorionic Gonadotropin*

AMENORRHEA, whether primary or secondary, is still a major therapeutic problem. With rare exceptions organotherapy has failed to elicit permanently good results. At best, bleeding is induced upon withdrawal of the experimentally administered hormone without, however, sustained cyclic menstruation thereafter. The ideal treatment has not been attained, because the etiology of amenorrhea remains unknown.

Recently Pencharz[1] reported maximum stimulation of the immature rat ovary with chorionic gonadotropin combined with diethylstilbestrol. The stimulation exceeded that of any other experimental hormonal stimulus. This combination of hormones was, therefore, given to 12 amenorrheic women in the hope that such therapy might effect more permanent results than were attained with cyclically administered sterols or with equine gonadotropins. The latter hormones had previously yielded very indifferent results in this clinic.

Of the 12 patients, 4 complained of primary and 8 of secondary amenorrhea; only 8 were treated and observed long enough to warrant reporting. All of these patients were sterile.

Method. In addition to the usual routine clinical data, urinary bioassays for gonadotropins (FSH) and estrogens, as well as endometrial biopsies were made before and 2 weeks after therapy was completed. These hormones were determined on 7 to 10 pooled specimens of 12-hour night urines. The estrogens were estimated by modifications of existing methods of assay on spayed adult rats. The gonadotropin was determined by the Zondek alcohol-precipitation method, using immature mice. Vaginal canalization, Graafian follicle stimulation, and vaginal cornification was taken as a positive response. Some pregnandiol determinations were made according to the method of Venning and Browne.

The B.M.R. of all of the 12 patients was below normal, varying from −15 to −28. Accordingly, thyroid extract was prescribed in doses of ½ to 2 grains daily with weekly intermittence each month to avoid cumulative effects.

Oral diethylstilbestrol was given, usually for 2 weeks in each month in 1 to 2-mg. daily doses, the lesser dosage being reserved for those who complained of nausea or other side reactions.

Chorionic gonadotropin (APL) was injected twice or thrice weekly in doses varying from 500 to 1000 I.U. for 2 months; after which injections were stopped for one month to lessen the possibility of anti-hormone effects.

A treatment schedule of 6 to 12 months in the above fashion was deemed an adequate trial.

Results. No severe side reactions were noted in any patient. Occasional headaches were induced and it was not clear which of the two hormones was responsible.

The essential diagnostic and therapeutic data are depicted in the accompanying table.

No striking advantages can be claimed for this trial therapy as compared with cyclically administered sterols or other gonadotropic treatment. One patient with primary, and 2 patients with secondary amenorrhea, have continued to menstruate from poorly developed endometria at long and irregular intervals, but not without occasional supplemental therapy with oral estrogens, such as diethylstilbestrol or the naturally conjugated estrogens.† The other patients were wholly refractory to treatment. Infertility was not influenced. Bioassay yielded no data of striking diagnostic or therapeutic significance.

Most of the values before and after the experimental treatment fall within normal limits. It is apparent, however, that the increased estrogenic titers following therapy were not of the same high level as seen at the mid or premenstrual phases of the normal cycle. In one case treatment seems to have actually depressed the values for estrogens. The values for the pituitary gonadotropic factor were not significant. They did not attain castrate nor menopausal levels. The experimental therapy did suppress FSH excretion in 3 cases.

The endometrium showed increased proliferation in all cases but never progestational reaction.

Comment. Most of the evidence here and elsewhere points to ovarian and endometrial refractivity to hormonal stimulation and until this refractory state is better understood, the problem of amenorrhea remains unsolved. It is apparent that fair amounts of circulating hormones may activate an atrophic endometrium, but this does not stimulate a true menstruation. It is possible that more concentrated dosage would have elicited better responses. But here again the intangible factors of variability of organ or species response to hormonal stimulation complicate the question of adequate dosage. This clinical experiment again emphasizes the fact that laboratory observations are not necessarily applicable to the human subject.

* This study was supported by a grant from Ayerst, McKenna and Harrison, Ltd.

[1] PENCHARZ, R. I.: *Science* 91: 554. 1940.

† The natural estrogen (Premarin) was supplied by Ayerst McKenna and Harrison, Rouses Point, N. Y.

Histological preparation and interpretation of the endometrial biopsies by Dr. J. Tragerman is gratefully acknowledged.

TABLE 1. DIAGNOSTIC AND THERAPEUTIC DATA ON 8 CASES OF AMENORRHEA

Name, Age, Type and Duration of Amenorrhea	Endometrial Biopsy Tissue		Bioassay of Urine				Therapy			Results and Comments
			Before treatment		After treatment					
	Before treatment	After treatment	FSH[1] R.U.	Estrogens R.U.	FSH R.U.	Estrogens R.U.	APL I.U.	Duration	Diethylstilbestrol mg.	
J.K. 31 (Primary)	Atrophic	Early proliferative	25	0	25	10.0	9,000	6 mo.	160	Diabetic eunuchoid with infantilism; withdrawal bleeding; limited breast and genital development
R.C. 27 (Primary)	Atrophic	Early proliferative	0	5.0	0	12.5	35,000	8 mo.	224	Withdrawal bleeding 3 times; limited breast and genital development
F.G. 21 (Primary)	Atrophic	Late proliferative	25–50	10.0	0	20.0	32,000	8 mo.	168	Pregnandiol excretion 6.6 mg.; irregular cycles since; occasional diethylstilbestrol necessary
F.H. 34 (Secondary) 4 yrs.	Atrophic	Early proliferative	0	5.0	0	7.5	54,000	9 mo.	252	Irregular cycles during 6 mo. following treatment; occasional diethylstilbestrol necessary since treatment
M.K. 30 (Secondary) 10 yrs.	Atrophic	Early proliferative	25	10.0	25	12.5	66,000	10 mo.	140	Latent luetic; withdrawal bleeding twice; none since
D.I. 31 (Secondary) 1 yr.	Early proliferative and some atrophic tissue	Late proliferative	25–50	20.0	0	20.0	72,000	12 mo.	168	Withdrawal bleeding with irregular cycles; occasional therapy with natural estrogen necessary since treatment
M.L. 18 (Secondary) 1 yr.	Biopsy not made	Biopsy not made	25	40.0	0	20.0	63,000	11 mo.	308	Benign adreno-genital syndrome; infrequent withdrawal bleeding
M.W. 30 (Secondary) 18 mos.	Early proliferative	Late proliferative	0	17.5	0	0	54,000	9 mo.	252	Withdrawal bleeding once; epistaxis twice

[1] FSH, pituitary gonadotropin

The problem of treating amenorrhea is no farther advanced after this therapeutic trial.

Summary. Twelve women complaining of amenorrhea were treated with diethylstilbestrol and chorionic gonadotropin for periods varying from 6 to 12 months. Only 8 patients were adequately observed. Withdrawal bleeding was induced, and a recurrence of bleeding could be sustained only with occasional supplemental treatment with diethylstilbestrol or natural estrogens.

It is concluded that the refractory state of the ovary and/or the endometrium underlying amenorrhea is not significantly influenced by treatment with combined chorionic gonadotropin and diethylstilbestrol.

S. J. GLASS

Endocrine Clinic,
Cedars of Lebanon Hospital,
Los Angeles, California

Androgen Therapy in Women

TO THE EDITOR:

FADS AND FASHIONS always have characterized the practice of medicine, indeed, even diseases are not free from these vagaries, as our old Professor of Medicine observed in a paper on 'Fashions in Typhoid Fever,' but unfortunately clinical endocrinology in recent years has had more than a healthy share of these. The past 12 years have seen extravagant therapeutic excursions involving the use of chorionic gonadotropin, equine gonadotropin and now the currently popular ones, androgens and diethylstilbestrol.

The organotherapeutist of several decades past did little harm and dubious good with his glandular potions regardless of his ardent empiricism or the woeful paucity of his pretherapeutic diagnostic endeavors. Now, however, there is not the same immunity for the careless or unscientific therapeutic enthusiast. Many of the currently available endocrine preparations are powerful pharmacodynamic principles, which, depending upon the skill of the clinician, may be implements for the repair of damaged glandular systems or may act as tools for wrecking completely the physiologic economy of patients.

The recent widespread employment of androgens in the treatment of many of the functional aberrations and organic diseases of women's gynecic system has gone too long undenounced as a deplorable example of highly dangerous empiricism. When carefully controlled scientific studies of the pharmacologic effects of androgens upon women were being reported by competent workers, there was the obvious justification that here was a new scientific gimcrack which was yielding stimulating experimental data. At the present time, however, with pharmaceutical concerns widely advertising androgens for use in gynecic disorders in this and other journals, conscientious and scientific clinicians cannot continue to dismiss placidly this victimization of women as being the result of natural 'growing pains' of a new science.

Despite the fact that, as yet, careful clinical studies have failed to identify a single syndrome in women due to a hypo-androgenic state, and regardless of the fact that no generally acceptable proof has been advanced as to the physiologic rôle of androgens in gynecic endocrinology, androgenic therapy continues to be a common practice. Why is this, we ask. Is it because clinicians find themselves unable to resist the commercial solicitations of pharmaceutical chemists who, having male hormones to sell, but embarrassed by such a limited field in andrologic practice, insist that these be used in gynecology?

Androgens have come to be used inseparably with estrogens under diverse circumstances, including prolonged and excessive uterine bleeding, menopausal symptomatology, undesired lactation, menstrual migraine, dysmenorrhea, cyclomastopathy, et cetera. Equally as good, and often better, symptomatic responses have been obtained in these conditions from the use of estrogens. The rationale of risking grave virilization sequellae from unnecessary androgenic therapy is incomprehensible.

Androgenic therapy is admitted by its proponents to produce for the most part 'ovarian negating' responses. Is the therapeutic implication that these conditions are hyperovarian ones? Most conservative gynecologists realize the need for adequate implements capable of stimulating hypofunctioning ovaries, upon the existence of which so many gynecologic aberrations are predicated. Wherein does there exist the need for the further depressing of these hypofunctioning ovaries?

Aggravation of ovarian failure, while a cogent contra-indication to the use of androgens in most gynecologic states, is not the gravest of these contra-indications. The most serious complication of androgenic therapy in the female is the cosmetic and contrasexual mutilation which it may produce. Any clinician practicing endocrine gynecology sees far more hirsute women than he can depillate, in fact, far more than he can conscientiously offer any therapeutic hopes. Why should this number be increased willfully by unnecessary therapy?

It may be argued that these virilization phenomena, if they do appear during androgenic therapy, will disappear upon its discontinuation. Some of these may disappear; others are irreversible. The excessive hair may fall slowly following cessation of therapy: all may not disappear. The laryngeal changes, responsible for the throaty, husky voice, do not leave the individual.

Some workers have justified the production of these distressing pseudohermaphroditical signs upon the basis of the therapeutic results obtained, i.e., relief from endometriosis, and shrinkage of fibromyomatous tumors. Admitting the fact that some gynecologists are possessed of a *furore operantivus*, and that under these circumstances, conservative endocrine therapy has been a boon to many women, surgery for endometriosis and for fibromyomata seems far more conservative than contrasexual hormonal mutilation of the woman.

This writer has seen a number of pathetic examples of unjustified androgenic therapy. The most pathetic and flagrant of these cases was the following.

The patient, a 15.5-year-old girl, was seen by a neurologist because of progressive muscular weakness of 2.5 years' duration. His diagnosis was that of progressive muscular dystrophy of the Landouzy-Dejerine type. The patient was referred by him to the writer because of a strange history of androgenic therapy having been employed previously and because of the obvious contrasexual effects of this. The endocrine record was as follows.

The patient's adolescence had been normal. Menarche had occurred at 13 years of age. Sexual maturation had been normal. Menses had continued regularly and without abnormal symptomatology until one year previously when the patient consulted a physician who is said to have started her on androgenic therapy. She is said to have received 25 mg. of testosterone propionate intramuscularly every 3 to 4 days for 10 months. One scanty menstrual period occurred following the initiation of therapy. No further menses occurred. The patient's voice became so husky she could hardly talk. There was noticeable regression in the breasts. There was some increase in bodily and facial hair. Acne became worse.

A wise family physician stopped this treatment 3 months before the patient was seen by us. Menses returned within a month after treatment was discontinued. Three months after treatment was stopped the patient still had a very husky voice, slight hirsutism, slight hypertrophy of the clitoris and a moderate atrophy of the uterus.

The only apparent foundation which the patient's physician had for initiating androgenic therapy of this little girl, who was obviously normal from a gynecologic and endocrine point of view, must have been that he had been told that androgens, among their various other pharmacologic properties, possessed the ability to stimulate the volume of skeletal muscles. It goes without saying that the androgenic therapy given this patient had no effect on her Landouzy-Dejerine paralysis.

From these considerations it seems obvious that any androgenic therapy of woman, regardless of what its presumed foundations may be, should be considered contraindicated and that, when this therapeutic approach be embarked upon, the patient is exposed needlessly to possible pharmacologic mayhem.

E. C. Hamblen, M.D.

Duke Hospital
Duke University
Durham, N.C.